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TUBERCULIN

A Report of a Conference on Its Standardization[1]

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INTRODUCTION

In June, 1925, the Surgeon-General of the United States Public Health Service received the following letter:

SOCIÉTÉ DES NATIONS — LEAGUE OF NATIONS

Health Section, Geneva, May 15, 1925

Dear Dr. Cumming:

As you may remember, the Health Committee has decided to undertake the standardization of tuberculin. The permanent Standard Committee

[1] Prepared by direction of the Surgeon-General, United States Public Health Service. Issued also as Supplement No. 57 to the Public Health Reports, Washington, Government Printing Office, 1926.

appointed a special Commission for this purpose, consisting of Professor Calmette (Chairman), Prof, Léon Bernard, Dr. Madsen and Dr. Tsurmi.

This Commission has come to the conclusion that before submitting proposals concerning the standardization of methods, it will be necessary to obtain as complete information as possible on the methods of preparation and titration in use at the various institutes producing tuberculin.

For the purpose of securing this information from the United States, I am sending you under separate cover the questionnaires and explanatory letters prepared by the Commission. I should be grateful if you would kindly transmit these forms to the producers of tuberculin in your country.

I am sure that the Commission will appreciate your assistance in this investigation.

With kind regards,

Yours very sincerely,
Ludwich Rajchman

Surgeon General Cumming, H.S.,
United States Public Health Service,
Washington, D. C.[2]

In July the Director of the Hygienic Laboratory transmitted this questionnaire with a series of additional questions to manufacturers of tuberculin in the United States. The answers were returned, in some instances slowly, so that it was not possible to correlate the information obtained until October of 1925.

On October 5, 1925, after consulting with the officers of the Bureau of Animal Industry and the Research Committee of the National Tuberculosis Association, the Surgeon-General sent out the following letter:

TREASURY DEPARTMENT
BUREAU OF THE PUBLIC HEALTH SERVICE
Washington
Office of the Surgeon-General, October 5, 1925

Dear ———:

The Public Health Service of the Treasury Department and the Bureau of Animal Industry of the Department of Agriculture, the official agencies concerned in the control of tuberculosis, and the National Tuberculosis Association, which also has a considerable interest in the subject, have carried on investigations for a number of years with the object of endeavoring to standardize the commercial preparations of tuberculin in the market. No very

[2] The explanatory letter and questionnaire mentioned in this letter will be found as *Appendix A* and *Appendix B* to this report.

conclusive results have been attained and the whole subject is in a distinctly unsatisfactory state.

That this is not peculiar to America is evident by the fact that at its last meeting the Health Section of the League of Nations designated a special committee on the standardization of tuberculin under the chairmanship of Professor Calmette of the Pasteur Institute, Paris. This committee has been collecting data wherever they were available, including the United States.

With the view of bringing to bear on this subject the views of a group well qualified to judge of the merits of the problems presented, and with the view of arriving at conclusions which may accompany the American report to the Committee of the League of Nations, it has been decided to call a conference for the purpose of discussing the subject, and, if possible, of arriving at conclusions.

The following men have been invited to attend the conference:

Dr. Theobald Smith, President of the International Union against Tuberculosis and President of the National Tuberculosis Association.
Dr. Ludvig Hektoen, past Chairman of the Medical Division of the National Research Council.
Dr. Reid Hunt, Professor of Pharmacology, Harvard University Medical School.
Dr. Marion Dorset, Chief of Bio-Chemic Division of the Bureau of Animal Industry.
Dr. George W. McCoy, Director of the Hygienic Laboratory, United States Public Health Service.
The Research Committee of the National Tuberculosis Association.

The material from which the conclusions will be drawn will be presented in the following way:

1. The present status of the manufacture and use of veterinary tuberculin in America. Dr. E. C. Schroeder, Director, Animal Experiment Station.
2. A discussion of the present methods proposed for standardization of tuberculin. Dr. Esmond R. Long, Assistant Professor of Pathology, University of Chicago.
3. The variations in these proposed standards apparent from the use of various pure substances used for tests. Dr. Max Pinner, Director, Serological Division of the Chicago Municipal Tuberculosis Sanitarium.
4. The principles of bacteriological chemical analysis: the application of these principles to commercial large-scale production applied to the tubercle bacillus. Dr. Treat B. Johnson, Professor of Chemistry, Yale University.

The meeting of the Council will be held at the Butler Building, 3 B Street, S.E., Washington, D. C., on October 16, 1925, at 10 A.M. The meeting will be opened by the Surgeon-General of the United States Public Health Service and Dr. John R. Mohler, Chief of the Bureau of Animal Industry. The results of the answers to the questionnaires sent out by the League of Nations will be presented by the Hygienic Laboratory.

This meeting is called by the United States Public Health Service, the

Bureau of Animal Industry and the National Tuberculosis Association. It is hoped that you will be able to attend the meeting. This meeting is not open to the public and is confined to the participants mentioned in this letter.

H. S. Cumming,
Surgeon-General, United States Public Health Service
John R. Mohler,
Chief, Bureau of Animal Industry
Linsly R. Williams,
Managing Director, National Tuberculosis Association

This letter called together, on October 16, 1926, a conference to discuss, for America, the question of the standardization of tuberculin and to obtain, if possible, definite conclusions which would guide American action in this matter and serve as a guide to the Health Section of the League of Nations in its discussion with regard to the American position.

THE MEMBERS OF THE CONFERENCE

At the conference, representing the United States Public Health Service, the Bureau of Animal Industry and the National Tuberculosis Association, were Surgeon-General H. S. Cumming of the United States Public Health Service (in the chair); Dr. John R. Mohler, Director of the Bureau of Animal Industry of the Department of Agriculture; Dr. A. M. Stimson, Assistant Surgeon-General of the United States Public Health Service; and Dr. Linsley R. Williams, Managing Director of the National Tuberculosis Association.

The Committee serving as a court of decision was composed of Dr. Theobald Smith, President of the National Tuberculosis Association; Dr. George W. McCoy, Director of the Hygienic Laboratory; Dr. Reid Hunt, Professor of Pharmacology, Harvard University Medical School; Dr. Ludvig Hektoen, past Chairman of the Medical Division of the National Research Council; and Dr. Marion Dorset, Chief of the Bio-Chemical Division of the Bureau of Animal Industry.

The Medical Research Committee of the National Tuberculosis Association was represented by Dr. William Charles White (Chairman), United States Public Health Service; Dr. Allen K. Krause, Johns Hopkins Hospital, Baltimore; and Dr. Paul A. Lewis, Rockefeller Institute, Princeton, New Jersey.

The active research work on which to base the discussion was presented by Dr. E. C. Schroeder, of the Bureau of Animal Industry Experiment Station; Dr. Esmond R. Long, Department of Pathology of the University of Chicago; Dr. Max Pinner, of the Chicago Municipal Tuberculosis Sanitarium; and Dr. Treat B. Johnson, Professor of Chemistry, Yale University.

CONCLUSIONS

The conclusions, which follow in answer to three questions, were based upon the subsequent papers and discussion:

Question: Have we sufficient knowledge at the present time to warrant the establishment of a standard for this substance?

Answer: We have not at present sufficient information to recommend definite changes in the standardization and testing of tuberculin as now practised by different countries, nor shall we have until the different methods proposed have been exhaustively studied comparatively.

Question: Can we, with our present knowledge, make important improvements in the present methods of manufacture of tuberculin and what should these improvements be?

Answer: The Commission believes that a test based upon the following definition will aid in bringing about a uniformity in practice:

Tuberculin O.T. should be defined as a product derived from bouillon cultures of the tubercle bacillus (human type) by filtration and concentration and should have the following essential characteristics:

a. It should cause typical symptoms of allergy (constitutional or skin reactions) in tuberculous animals and at the same time be without effect on normal animals.

b. Its potency should be sufficient to cause the death of tuberculous guinea pigs within 24 hours after intraperitoneal injection of 0.25-gm. doses per 500 gm. of guinea-pig weight.

In practice the strength of other forms of tuberculin should be computed in terms of O.T.

Tuberculin from bovine strains of tubercle bacilli should conform to the standard for O.T. (Old Tuberculin).

Tuberculins from avian strains of tubercle bacilli do not conform to the standard for O.T. and should be considered independently. It is desirable for Government Bureaus concerned with licensing tuberculin to issue a state-

ment of a method with which a product of suitable potency and purity is more or less uniformly obtainable.

Question: What lines of study are the best for us to pursue to enable us to arrive at a better standard of tuberculin?

Answer: The Commission unanimously approves the present coöperative plan of research being carried on by the Research Committee of the National Tuberculosis Association in coöperation with the Hygienic Laboratory of the United States Public Health Service and the Bureau of Animal Industry as the most likely procedure to bring about a better understanding of tuberculin and its action, and enable us to arrive at better methods of use and standardization, and the Commission urges that this work be continued.

SCIENTIFIC PAPERS

SURGEON-GENERAL CUMMING (*calling the meeting to order*): It is a great pleasure for me to welcome the members of this conference on the standardization of tuberculin. Every member of it was carefully chosen to represent some broad phase of the biological problem presented by this diagnostic and therapeutic agent—tuberculin.

Study in America has progressed very rapidly, both in the Bureau of Animal Industry and through the researches being carried out by the Research Committee of the National Tuberculosis Association, but it is doubtful whether this conference would have been called at this time had it not been for the urge given it by a questionnaire sent out to all countries, including the United States, by the Health Section of the League of Nations looking toward some action in an endeavor to standardize tuberculin.

As you all know, we have no official relation to the League of Nations, but so many interests, both human and industrial, are involved in fixing an international standard of this sort that it seems wise to attempt to formulate an American opinion on the subject both for our guidance and for presentation to the Health Section of the League.

The Biological Law[3] in the United States places under our jurisdiction the licensing of all serums, viruses and toxins which have to do with the prevention and cure of disease in man. In the matter of tuberculin this is a very small matter compared with the enormous use of this substance in animal industry, for which the Bureau of Animal Industry of the Department of Agriculture is responsible. In order to bring together

[3] Regulations for the Sale of Viruses, Serums, Toxins. Miscel. Pub. No. 10, U. S. Public Health Service, Government Printing Office, Washington, 1923.

for your consideration the most recent work on the subject, the Bureau of Animal Industry and the Public Health Service have united in asking the Research Committee of the National Tuberculosis Association to join them, and these three bodies are represented in the material which will be presented to you.

Dr. Mohler, who will welcome you, following me, will present the facts which are represented by the work of the Bureau of Animal Industry, with some suggestions as to the benefits which may result from this conference.

There is before you a synopsis[4] of the answers received in connection with the accompanying questionnaire sent out by the Health Section of the League of Nations. It would seem quite within the range of possibility that the conclusions reached here may fittingly answer these questions which would be of great service to all who have to deal with this problem:

1. Have we sufficient knowledge at the present time to warrant the establishment of a standard for this substance?

2. Can we, with our present knowledge, make important improvements in the present methods of manufacture of tuberculin and what should these improvements be?

3. What lines of study are the best for us to pursue to enable us to arrive at a better standard of tuberculin?

What an enormous factor tuberculin plays in animal industry will be apparent to you from Dr. Mohler's remarks. I should like in closing this welcome to comment upon the coöperation here represented of the two great government bodies dealing with this question and the voluntary organization, the National Tuberculosis Association. The coöperation of these bodies should soon result in a completion of our knowledge of this question; and, it may be that, if your conclusions to-day outline a feasible programme, you may, yourselves, have the opportunity of listening to the finish of the programme and the settling of this question in America.

Dr. Houck, the Assistant Director of the Bureau of Animal Industry, tells me that Dr. Mohler cannot be present but that he will present Doctor Mohler's remarks. Dr. Houck.

[4] This synopsis will be found as *Appendix C* to this report.

TUBERCULOSIS OF LIVESTOCK

U. G. HOUCK

Assistant Director, Bureau of Animal Industry

I regret that Dr. Mohler cannot be here himself, but he was suddenly called out of town on a court summons and requested me to present his remarks. This I shall do, and I have taken the liberty of adding a few of my own.

The eradication of tuberculosis of livestock in the United States is a feasible though huge undertaking. This work is important from an economic standpoint and also because a certain percentage of human tuberculosis, especially among children, is due to infectious dairy products obtained from tuberculous cows. Much progress already has been made through coöperative Federal and State efforts. Experience has shown that the "area plan" is the most economical method of eradicating bovine tuberculosis. In carrying out this plan all cattle in a county or other prescribed area are tested during an intensive, systematic drive. The "accredited herd method" is favored next from the point of economy and effectiveness. It has been observed that when this disease is eradicated from the cattle in a community it disappears or is greatly reduced among swine. Fowls also are susceptible, and eradication of tuberculosis from our poultry flocks is now receiving consideration.

Over seven million cattle in 607,000 herds were tuberculin-tested in the United States during the last year. The total number of reactors was 214,491 cattle, or about 3 per cent. In other words, tuberculosis was found in the proportion of one-third of an animal in every herd tested. It is self-evident that it is more economical to sacrifice one-third of an animal per herd now than to allow the disease to spread until 50 per cent or more of the animals per herd become tuberculous, as is the case in some European countries. If, by taking one-third of an animal now from every herd in this country, tuberculosis will be eradicated, the expense will not bankrupt the livestock industry, nor will it be too much for the State and National Governments to bear.

There are now 72,283 herds, containing 1,275,063 cattle, in the United States officially accredited as free from tuberculosis, an increase over last year of over 24,000 herds containing more than 354,000 animals. This is an increase of 49.9 per cent in accredited herds during the past year.

There are 921,758 herds, containing over eight million animals, that have passed one clean test. This is an increase over last year of 392,000 herds containing more than three million cattle.

At the present time there are under direct supervision over one million herds of cattle containing more than eleven million animals, and we have a waiting list of owners of 403,000 herds containing 3,500,000 cattle, who have voluntarily requested the coöperating forces to test their animals.

In the fiscal year, 1924, there were 38 counties placed on a "modified accredited area" status, and in 1925 additional counties were similarly placed to the number of 51, making a total of 89 accredited counties. There are in the process of being placed on a "modified accredited area" status a total of 591 counties which is an increase of 273, or 46 per cent, over last year.

A total of 726 veterinarians are now employed in the tuberculosis eradication work as compared with 565 a year ago. This force is divided as follows: Bureau of Animal Industry, 219; States, 246; counties, 261.

The various State legislatures that met during the past winter increased the total State appropriations available for the payment of indemnities from $6,000,000 to more than $11,000,000. It is expected, therefore, that there will be a considerable increase in the total number of cattle tested during the period provided for by most of the legislatures. It is further expected that the States will assume the responsibility of conducting the compaign in each Commonwealth, so that the Federal Government will thereby be relieved of the responsibility of controlling and eradicating tuberculosis of livestock in each State. This is a duty that manifestly belongs to the officials and livestock owners of each State. It is fit and proper that the Federal Government should act in an advisory way and help to work out the problem for the States; but until each State has an organization, feels the responsibility, and performs the work of controlling the disease, we shall fall far short of accomplishing the ideal results. The peak of tuberculosis eradication work will be reached within the next few years, after which there should be a gradual decline in Federal appropriations and the responsibilities that are now shouldered by the Department.

The data given show the magnitude of our field operations, which are based on tuberculin as the diagnostic agent. The Bureau of Animal Industry is the largest producer of tuberculin in the United States. In 1922 it produced 2,977,800 cc. to carry on these field operations; in 1923

the production was 2,639,750 cc.; and in 1924 it was 3,121,600 cc., which is about five times the combined output of all other producers. And it is expected that the Bureau's production will be increased considerably during the current year and probably for years to come.

In addition to the Biological Law, to which Surgeon-General Cumming alluded, the Virus-Serum-Toxin Law, approved on March 4, 1913, is in operation in this country. The Department of Agriculture is charged with the responsibility of administering this law. It gives protection to producers and also to those who use tuberculin in the field of animal industry.

Producing establishments engaged in interstate trade operate under licenses granted, and regulations and a system of inspection prescribed, by the Secretary of Agriculture. It is needless to enter into the details of the Virus-Serum-Toxin Law, as no doubt you are familiar with the purposes and provisions which extend even to include imported virus, serum, toxin and analogous products intended for use in the treatment of domestic animals.

In discussing the subject of fixing an international standard for tuberculin we should keep in mind the study and research that have been completed and what we really know on the subject. The Bureau is principally interested from an economic standpoint, and in view of our present knowledge of tuberculosis and tuberculin it seems that our extensive laboratory and field operations are being conducted on a practical, effectual working basis.

There seems to be no doubt that a free discussion of the three questions presented by the Surgeon-General in his address will lead to a fitting conclusion.

SURGEON-GENERAL CUMMING: Dr. Schroeder will now present his paper on "The Present Status of the Manufacture of Veterinary Tuberculin."

THE PRESENT STATUS OF THE MANUFACTURE OF VETERINARY TUBERCULIN

E. C. SCHROEDER

Director, Animal Experiment Station

In accordance with where and by whom it is made, tuberculin for veterinary use in the United States may be classed under three headings, *Federal*, *State* and *Commercial*.

The *Federal*, commonly spoken of as Bureau of Animal Industry tuberculin, is made in the Biochemic Division of the Federal Bureau of Animal Industry, and is estimated to be about 90 per cent of the total amount. I have been informed that a million or more doses are made and distributed monthly. As Dr. Marion Dorset, Chief of the Biochemic Division, under whose direction and supervision this tuberculin is made, is present at this Conference, I will leave it to him to give, if necessary, a more detailed account of its preparation and distribution.

State tuberculin is prepared in the laboratories of State Livestock Institutions in a number of States. It is used exclusively within the States of its origin, and therefore the Federal Government has no authority to supervise its production, purity and potency, and little definite information regarding it is available. Occasionally samples are sent to the Bureau of Animal Industry at Washington to be tested, in most instances after some question has arisen about their quality, and the tests made with such samples prove that State tuberculin is not invariably as good as it should be. For example, quite recently a sample was received which was claimed to have caused reactions in an exceptionally large number of cattle in which no lesions of tuberculosis were found on postmortem examination. This specimen had a faintly clouded appearance, and with it quite an abundant sediment was obtained in centrifuge tubes. Microscopic examination of the sediment revealed a large number of presumably dead, acid-fast bacteria and an enormous number of micrococci. It is hardly necessary to say that a tuberculin heavily contaminated with extraneous bacteria may cause reactions resembling tuberculin reactions in animals wholly free from tuberculosis.

All States in the United States do not produce tuberculin for veterinary use, and the methods of production in different States are not identical.

Commercial tuberculin for veterinary use is made in the United States under license issued by the Bureau of Animal Industry by twelve biochemical concerns. The total amount produced last year (1924) was 2,036,854 doses, divided as follows: for cutaneous use, 1,617,122; for subcutaneous use, 316,456; liquid for ophthalmic use, 80,137; and ophthalmic discs, 47,559.

As nearly as it is possible to estimate, the above enumerated doses amount to from 225,000 to 250,000 gm. of Koch's Old Tuberculin.

Each concern licensed by the Bureau of Animal Industry has on file in the Virus-Serum Division of the Bureau a statement regarding the preparation of its tuberculin. A study of these statements shows that com-

mercial tuberculin is marketed under several different names and forms, as follows:

Subcutaneous tuberculin, in most cases a diluted tuberculin, of which each cubic centimetre contains 0.125 gm. of Koch's Old Tuberculin. The Bureau of Animal Industry requires that each subcutaneous dose of tuberculin for a bovine animal of average size must contain the equivalent of 0.5 gm. of Koch's Old Tuberculin.

Intradermic tuberculin, the same as subcutaneous with the exception that it is doubly as strong; that is, each cubic centimetre contains 0.25 gm. of Koch's Old Tuberculin.

Purified intradermic tuberculin, an alcoholic precipitate of Koch's Old Tuberculin dissolved in physiological salt solution.

Ophthalmic liquid, practically the same as the purified intradermic tuberculin.

Ophthalmic discs, alcoholic precipitate of Koch's Old Tuberculin, washed, dried, ground, mixed with milk sugar, boric acid and bicarbonate of soda and pressed into discs.

Retest tuberculin, same as subcutaneous with the exception that each cubic centimetre contains 0.375 in the place of 0.125 gm. of Koch's Old Tuberculin.

The statements show many variations in the methods of preparation. One concern depends entirely on a single human strain of the tubercle bacillus; another on a single bovine strain; others use two or more strains, usually a mixture of human and bovine; one uses as many as seven and one as many as ten strains.

The medium on which the bacilli are grown varies greatly, both in composition and initial reaction. Veal bouillon, beef bouillon, bouillon made with meat extract, etc., are used, and the percentage of glycerine varies from 3 to 7.

The length of time the cultures are incubated varies, as does also the relation between the volume of medium and its surface area; the temperature at which the tubercle bacilli are killed varies, not only in degrees but also in the duration of exposure. In most cases Arnold steam sterilizers are used; in one case sterilization in an autoclave under steam pressure is practised; and in one discontinued or interrupted exposure to heat.

The methods of filtration, precipitation when it is used, the character of the flasks in which the cultures are grown, the methods of testing purity and potency, the preservatives added, etc., all show variations.

Taking this failure of more precise agreement in methods of production among different commercial concerns into account, and the fact that

actual tests of commercial tuberculin show that most of it is satisfactory for veterinary purposes, leaves no doubt that tuberculin is a substance which can be subjected to much harsh treatment and many trying vicissitudes without losing its virtue as a diagnostic agent for tuberculosis.

It now remains to say a few words about the importance of veterinary tuberculin.

A report for September, 1925, which gives a summary of the bovine tuberculosis eradication work of the Federal Government in coöperation with various States, shows that 1,231,692 herds, which number 12,302,200 cattle, are now under supervision. These large numbers are constantly increasing and, for some time to come, most of the cattle they represent should be tested with tuberculin once *per annum*.

The bovine tuberculosis eradication project in the United States is progressing along two lines, namely, accredited herds and accredited areas. An accredited herd is one in which three successive semiannual, or two successive annual tuberculin tests have been made without a reaction. An accreditation certificate is good for one year only, and its periodic renewal is made dependent upon an annual tuberculin test of the accredited herd without a reaction.

An accredited area is one in which, as determined by the tuberculin test, not more than 0.5 per cent of the cattle are affected with tuberculosis. At what intervals of time the cattle in such areas are subjected to the tuberculin test I am not quite sure; I believe there is a difference in different localities.

As the bovine tuberculosis eradication work progresses, we will have a constantly increasing number of cattle in the United States that must be tested periodically. The number tested under the supervision of Federal Inspectors and State Officials during last September (1925) was 665,627, among which 25,198 reacted. During last August (1925) the number was 676,856, with 19,066 reactions.

While the proportion of cattle affected with tuberculosis varies greatly in different States, it is now estimated that not more than 3 per cent, probably a little less, of the total cattle of the United States are tuberculous. Compared with the countries of western Europe, in some of which the proportion of tuberculous cattle is from ten to fifteen times greater, this is a very favorable condition. But, nevertheless, with the tuberculin testing now in progress in the United States, it means the annual condemnation and slaughter, on the basis of what the test reveals, of from 225,000 to 250,000 head of cattle, the value of which, estimated by using

the average per head value of the cattle on American farms, given in the last *Yearbook* (1924) of the U. S. Department of Agriculture (1924), is between eight and nine million dollars.

The tuberculin testing is being done by Federal and State Inspectors and so called accredited veterinarians. The latter are veterinary practitioners who have supplied evidence that they are qualified and can be trusted to make tuberculin tests.

It is the State inspectors and accredited veterinarians through whom, I assume, the State and commercial tuberculin comes to usage, and, as this means that State and commercial tuberculin is an agent used to test several million cattle annually, no doubt can be entertained that it is urgently necessary that it should be pure and potent.

In cattle testing we must aim, first of all, to ensure that the tuberculin used is amply potent. A standard potency, no doubt desirable, has not been proved to be essential, since cattle that are free from tuberculosis do not react when they receive subcutaneous or intravenous injections of eight to ten times the quantity of tuberculin required to cause a reaction in a tuberculous animal, and are in no discoverable way harmed by such large doses. The harm suffered by tuberculous cattle from excessive doses has not proved serious enough to give it economic importance, in part because a tuberculin reaction is equivalent to a condemnation which terminates the usefulness of the animal.

The expression, "doses of tuberculin," may be misleading when the number of doses distributed for veterinary use is compared with the available records of the number of animals tested. The discrepancy in this instance is explained by the fact that a very large proportion of the tested animals are subjected simultaneously to two or more tests, as, for example, the intracutaneous and the subcutaneous; the intracutaneous and a test somewhat similar to the intracutaneous, in which the tuberculin is injected into the vulval lips at the junction of the mucosa and skin; the intracutaneous and the ophthalmic, etc.; and in making the ophthalmic test it is a common practice to introduce into the conjunctival sac, first, what is designated as a sensitizing and later a test dose of tuberculin. The intracutaneous test, made by injecting tuberculin into the delicate skin of the tail, is the most commonly used in the United States.

In addition to the importance veterinary tuberculin derives in the United States from its extensive use, it has a further importance due to the fact that no method of controlling or eradicating tuberculosis among the lower animals has been devised which can hope to be successful with-

out its use at some stage. Tuberculous cattle often become dangerous disseminators of tubercle bacilli long before their health is determinably impaired or recognizable symptoms of disease have developed; and, even when other methods than tuberculin testing and the slaughter of reacting cattle are used, such as the Bang method of feeding calves pasteurized milk, or methods which depend upon physical examinations, milk examinations, etc., they must eventually turn to tuberculin to measure the progress that is being made and to distinguish with reasonable certainty between safe and dangerous animals.

A few words on the reliability of the tuberculin test as applied to cattle may not be amiss.

As practically all cattle that react with tuberculin in the United States are killed and examined postmortem, we have millions of animals from which we can determine the reliability of the tuberculin test, as far as this depends upon the presence of tuberculous lesions in animals that react. Quite recently I had occasion to study the data, and found that something less than one reacting animal among every four hundred tested cannot be proved to be tuberculous by the discovery of microscopic lesions of the disease in its body. Such so called "no-lesion tuberculin-reacting animals," in about one case out of every four, by searching microscopic examinations and guinea-pig inoculations, have been proved to be actually infected with tubercle bacilli; that is to say, have been proved to be early cases of tuberculosis. Hence, the reliability of the tuberculin test, as far as it is affected by reacting animals in which no lesions of tuberculosis can be discovered on autopsy, is better than 99.75 per cent.

To what extent the tuberculin test is unreliable because of the failure of tuberculous animals to react with it, is a more difficult question to answer, as the number of animals, which do not react and are killed early enough after the test to exclude errors due to subsequent infection, is quite small.

At the Experiment Station of the Bureau of Animal Industry, where all cattle are currently tested with tuberculin and eventually subjected to fairly careful postmortem examinations, we have practically no records of animals, never previously exposed to tuberculin, which failed to react and were afterward found, without subsequent definitely known or intentional exposure to infection, to be affected with tuberculosis. In other words, if an animal fails to react with tuberculin the first time it is tested, the experience of the Bureau's experiment station strongly indi-

cates that it is certainly free from tuberculosis. The station's experience in this respect extends over a period of more than a quarter of a century and concerns several thousand head of cattle.

Failure of tuberculous animals to react when the tuberculin test is applied a second, third or fourth time, is another matter. There are tuberculous animals which react once and never again, and the station has had a number of cattle under observation which reacted with two, three or four semiannual tests, and thereafter were so tolerant for tuberculin that large doses injected subcutaneously, intraäbdominally or intravenously caused no perceptible reaction.

This failure of a tuberculous animal to react with tuberculin must not be mistaken as evidence that the disease has been arrested. A number of such animals kept under observation to determine what the course of the disease would be, without ever regaining their sensitiveness for tuberculin, eventually died of tuberculosis, and nothing was observed in the course of the disease or during the autopsy at its termination to offer an explanation for the lack of tuberculin sensitiveness.

If the statements made by some of our bovine tuberculosis eradiacation inspectors are reliable, it is amazing how small the dose that deprives a tuberculous animal of its tuberculin sensitiveness is in some instances. I have been told that some tuberculous cattle lose their sensitiveness after a single intracutaneous dose.

Of course, it is well known that occasionally a far-advanced, usually physically evident, case of tuberculosis among cattle is wholly lacking in tuberculin sensitiveness.

The greatest weakness of tuberculin is that it gives us no clue to the age, extent, character or location of the tuberculous lesions in the bodies of reacting animals; and the fact that tuberculous animals, after one or more exposures to tuberculin, may wholly lose their tuberculin sensitiveness, justifies the slogan, "Once a reactor an animal must thereafter always be looked upon as tuberculous."

I believe that is all I need say on the subject of veterinary tuberculin at the present time.

SURGEON-GENERAL CUMMING: Dr. Long will give us a "Discussion of the Present Methods Proposed for the Standardization of Tuberculin."

DISCUSSION OF THE PRESENT METHODS PROPOSED FOR THE STANDARDIZATION OF TUBERCULIN

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I have been asked to discuss some of the principles underlying the standardization of tuberculin, and to say something concerning the large-scale production of tuberculin from synthetic media. We must admit at the outset that we do not know the nature of the active principle of tuberculin. At present the only definition we can make of tuberculin is "that substance which elicits what by common consent is called the 'tuberculin reaction.' "

The ideal method of measuring the strength of a tuberculin preparation would be a chemical one. Unfortunately, at present we are not sufficiently well acquainted with the chemical nature of the active principle to make use of a chemical method for standardization. However, work is under way in a number of laboratories which may ultimately make such a method possible. At the very least it may be possible to standardize the production of tuberculin chemically in a standard medium of known chemical composition. I understand that Dr. Dorset in the Bureau of Animal Industry uses such a medium to great advantage, and I have devised one on which two large pharmaceutical houses, which are coöperating with the Research Committee of the National Tuberculosis Association, have prepared huge quantities of tuberculin for research purposes.

The important ingredients of this medium are asparagine, ammonium citrate and glycerol, with acid and alkaline salts present in such amount that the medium is buffered and requires no titration. As the medium contains no protein originally, chemical methods, based on the amount of protein occurring in such media after growth of tubercle bacilli, may yield some information as to the potency of such preparations, and the bacilli grown are produced in a standard way, permitting the isolation of important products of uniform character. As will be brought out by Dr. Johnson later, some of these products have high tuberculin activity. In the development of this field there is much prospect for advance toward chemical standardization.

At present, however, in the lack of definite knowledge on the chemical nature of the active principle of tuberculin, we must continue with bio-

logical methods of standardization, that is, methods based on the tuberculin reaction itself. The tuberculin reaction is an allergic reaction, or reaction of hypersensitiveness, and the standardization of tuberculin is based in most laboratories on the hypersensitiveness of the tuberculous guinea pig. Both the general and the local reactions have been used in the evaluation. Recently the antigenic capacity of tuberculin in the precipitin and complement-fixation reactions with the serum of tuberculous animals has been proposed as a measure.

The advantages and disadvantages of the methods outlined above may be conveniently analyzed under four headings: (1) the methods based on the lethal dose for the tuberculous guinea pig, (2) the method based on the cutaneous test, (3) the complement-fixation method of Watson and Heath, and (4) the precipitin method of Dreyer and Vollum.

Methods based on the lethal dose for the tuberculous guinea pig: The original Koch standardization, the Frankfurt method and the method of the United States Bureau of Animal Industry are to some extent similar in their advantages and disadvantages.

The Koch method has the advantage of extreme simplicity. A preparation of tuberculin passes the test or fails, according as 0.5 cc. kills or fails to kill a tuberculous guinea pig. Practically no labor is required, and the test needs only 30 hours for its completion.

The disadvantages, however, are marked. In the first place, the test is too gross. The criticism applies equally to all methods based on the lethal dose for the tuberculous guinea pig. There are too many unknown factors. A positive result, the death of the guinea pig, represents the summation of these unknown factors. The first unknown factor is the extent of the tuberculosis itself within the guinea pig. The animal is already absorbing a great or small amount of poisonous material, as the course of the disease present is rapid or slow. The general tuberculin reaction is added to this unknown factor. The general tuberculin reaction includes the summation of the individual tuberculin reactions between sensitized tissue and tuberculin in all parts of the body. Probably all tissues are sensitized to some degree, but the degree for the different tissues is not known. There is evidence that it varies in the different tissues (unpublished observations of the author on the suprarenal, kidney, testis and skin). Perfection in a test based on the strength of the general reaction could not be obtained without a series of animals of the same weight, with exactly the same amount of tuberculosis at the time of the test, with livers, spleens, brains, kidneys, etc., of the same

size, with the same amount of muscle, the same amount of skin and subcutaneous tissue, etc. This is obviously impossible of attainment. Even when a large series of animals is used, accordingly, and a lethal effect on the majority is considered the basis for a standard, individual variation is so great as to rob the test of much of its value.

There is another weighty objection. The test is quantitative only in a "pass or fail" manner. No unit is established. A unit is very desirable, not only in the diagnostic, but particularly in the therapeutic use of tuberculin. Two preparations of tuberculin might pass the test, and yet one of them be twice as potent as the other. This opens the possibility of gross error in therapeutic dosage.

The Frankfurt method has the advantage of relative simplicity, and recognizes the variability of animals as respects the lethal dose, without, however, avoiding it. An advance over the Koch procedure is achieved, in that an attempt is made to measure the degree by which superstrength preparations surpass the standard, and a basis is set for dilution to a common strength. However, no true unit is established by which the strength of a preparation may be determined without going through the laborious process of comparison with a standard tuberculin on a large series of animals.

The method of the United States Bureau of Animal Industry is an improved lethal-dose method, in which careful control is exercised with respect to the degree of sensitiveness of the animals used. The actual measurement of tuberculin is made only after extended preliminary tests have led to the selection of animals of suitable and comparable sensitiveness. The method is, however, laborious, and large numbers of animals are required, a great many being killed in the determination of sensitiveness before the test proper is begun.

At the best, even when well controlled and based on averages, methods founded on the lethal dose leave much to be desired, in view of the unquestionable complexity of the general tuberculin reaction. The method of the Bureau of Animal Industry, like the other methods of this type, sets up a required standard which must be met before a tuberculin is acceptable, but it does not establish a unit which can be used in measuring doses.

In favor of the lethal-dose methods in general, in contrast to the serum methods discussed below, is the fact that the allergic state of the tuberculous animal is a factor in the measurement. It is the allergic state of the patient or suspected animal which is of significance in the diagnosis

and treatment of tuberculosis by tuberculin. There is therefore in these methods no such dissociation of standardizing principle and diagnostic and therapeutic action as in the serum standardization tests analyzed below.

The intracutaneous test of Lewis and Aronson: This test, based on the intracutaneous test of Roemer, has the great advantage of close association between the standardizing test and the use to which the product is adapted. The substance is standardized with respect to the skin of an allergic animal and later used on the skin of an allergic patient. Furthermore, it is easy of application, requires no special technique, takes little time, and is economical of animals.

It would perhaps be the mose useful method were it not for one serious defect. The reactive capacity of the skin varies tremendously in a series of tuberculous guinea pigs, even when these are all injected at the same time. Numerous authors have stressed this point, and Lewis and Aronson themselves are careful to state, on the basis of their own protocols: "It is evident that the individual variation in reaction of the animals is wide." Naturally, the value of a test in which the strength of reaction is an important measuring factor, is much reduced by such variability.

To the present methods based on the allergic response in the tuberculous guinea pig I have added one in which the hypersensitiveness of the germinal cells of the tuberculous animal is used as the "measuring rod" for tuberculin activity. This type of tuberculin reaction I have described in the literature as the "testicle tuberculin reaction" and more recently as the "spermatocyte reaction." The high degree of susceptibility of the germ-cells of the tuberculous guinea pig to the action of tuberculin makes the testicle tuberculin reaction one of great delicacy. The reaction is specific for tuberculin. Other substances do not elicit a tuberculin type of reaction in the testicle of the tuberculous guinea pig, and tuberculin does not cause any reaction in the testicle of the normal guinea pig. On the basis of the change observed microscopically in the testicle of the tuberculous guinea pig which has been injected with tuberculin, the strength of a tuberculin preparation may be evaluated.

This method defines a "spermatocyte unit" of tuberculin as that quantity just sufficient to abolish spermatogenesis on injection in a volume of 0.1 cc. into the testicle of a 400-gram guinea pig with a mild, localized tuberculosis of one month's duration. Potent preparations of Old Tuberculin average about 10,000 units by this method. The method is new

and will, of course, have to be submitted to extensive trial before its advantages and disadvantages can be fully determined.

The complement-fixation method of Watson and Heath: This method has the primary advantage that it furnishes a unit in which all doses of tuberculin can be measured. It has another great advantage in that a standard reagent, the antiserum, can be prepared in a quantity sufficient for a great number of tests. The antiserum appears to stand aging moderately well, and thus furnishes a reagent of somewhat greater reacting constancy than the tuberculous guinea pig. It is time-saving in that the test may be carried out at once, upon the receipt of the material to be tested. No delay for the sensitization of guinea pigs is required.

On the other hand, it suffers from the great defect of complete dissociation of standardizing test and the use to which the material is adapted. There is no evidence that the tuberculin reaction and the antibodies which can be detected in the serum are even related. In fact, Calmette,[5] on the basis of long study, states that purified tuberculin will not act as antigen in the serum test. If this is true, the extraordinarily close agreement obtained by Watson and Heath, using the complement-fixation method, and Schroeder, using the lethal-dose method, is nothing more than a coincidence, and leaves open the possibility that samples of tuberculin might be encountered which would fix complement well in the presence of the antiserum, and yet be low in tuberculin potency. Indeed, if Calmette's contention is correct, a highly purified tuberculin, free from certain extraneous products of the tubercle bacillus which are antigenic to the antiserum, would fail altogether to give the complement-fixation test. Evidence corroborating Calmette's view is cited in discussing the precipitin method of standardization.

The precipitin method of Dreyer and Vollum: Like the fixation method just discussed, the precipitin method has the advantage of establishing a unit in which dosage can be calculated. Similarly, the essential reagent, the antiserum, is one which can be prepared in large quantities and which is of constant potency for a given lot. It has an advantage over the other serum procedure in that the precipitin method requires fewer fresh reagents and is easier of application.

On the other hand, as in the case of the fixation method, no relation has yet been established between the type of reaction in which the sub-

[5] *L'infection bacillaire et la tuberculose, 1922, p. 576.*

stance is actually used and that used in standardizing the product. In this case, also, the work of others indicates that the two reactions do not measure the same thing (Calmette[6]). The antiserum is not an antituberculin. It is more than possible that potent tuberculins might be encountered giving a weak precipitin test, and *vice versa*. In this case, also, highly purified tuberculins might be expected to give a weaker result than crude tuberculins. The reason for this is the simple fact that the serum prepared is an antiserum, not to the active principle of tuberculin alone, but to all the antigenic proteins of the tubercle bacillus. Until there is proof that all of these proteins are potent as tuberculin, the use of such a method of standardizing tuberculin is illogical.

The confusion which has existed concerning the relation of the tuberculin skin test and serum antibody reactions in tuberculosis has been considerably reduced by the recent studies of Zinsser and his colleagues, Julia T. Parker, Wayman and Mueller. By a method of extraction of tubercle bacilli, precipitation of the extract with acetic acid, and filtration, these investigators have secured clear solutions antigenic in both the skin test and serum antibody reactions with tuberculosis serum. At first they were inclined to believe that the two actions were due to the same active principles; but in a recent report on the continuation of this work, Mueller[7] states, "It has finally been possible to show definitely that they (precipitin reaction with tuberculosis serum and the tuberculin skin test) are dependent upon entirely different substances in the tuberculin." Mueller is of the opinion that the substance active in the precipitin test is a carbohydrate analogous to the gum found by Dochez and Avery to be active as an antigen with antipneumococcus serum, while he thinks that the substance active in the tuberculin skin test is chiefly protein.

In conclusion, I wish simply to say that in my opinion a biological standardizing method should be based on a type of true tuberculin reaction. The evidence offered in support of the serum methods of standardization is not sufficient to prove that these methods and those based on a true tuberculin reaction are measuring the same thing. Which one of the standardizing methods based on the allergic tuberculin reaction is most suitable is a matter for debate. I hope that, some time,

[6] *L'infection bacillaire et la tuberculose, 1922, pp. 573–574.*
[7] *Proc. Soc. Exper. Biol. & Med., 1925, xxii, 219.*

facilities can be afforded for large-scale comparison of the value of the several methods proposed.

SURGEON-GENERAL CUMMING: Dr. Pinner will give us "The Relation of Serological Reactions and Tuberculin Activity in Derivatives of Tubercle Bacilli."

THE RELATION OF SEROLOGICAL REACTIONS AND TUBERCULIN ACTIVITY IN DERIVATIVES OF TUBERCLE BACILLI

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It is the purpose of this report to present evidence from the literature and from our own work to prove that serological methods, such as precipitation and complement fixation, are unsuitable for the standardization of tuberculin. Besides accuracy, sensitiveness and specificity, an acceptable method for the standardization of tuberculin must be applicable to any substance derived from tubercle bacilli which has any tuberculin effect on tuberculous animals and not only to Old Tuberculin.

With various tubercle-bacillus preparations, complement fixation, precipitation and allergic reactions in tuberculous guinea pigs were performed.

The following methods were used in this work:

1. Complement fixation was done with an antisheep serum, using 2 hemolytic units of amboceptor and 2 units of complement. The anticomplementary titration was done with saline solution instead of serum; in the antigenic titration pooled serum of at least 3 tuberculous patients was used, each serum giving a four-plus fixation with our routine antigen. Having thus determined the anticomplementary and the antigenic unit of each preparation, the antigenic quotient was determined by dividing the anticomplementary by the antigenic unit. This antigenic quotient is a numerical expression of the so called range, and has proved in a large series of preparations a reliable indicator of the antigenic activity in complement fixation. This empirical finding receives further support from the fact that in more than 80 preparations tested so far it was found, as a general rule, that the antigenic quotient increases with decreasing antigenic unit. This is shown in table 1.

TABLE 1

PREPARATION	ANTIGENIC UNIT	ANTIGENIC QUOTIENT	PREPARATION	ANTIGENIC UNIT	ANTIGENIC QUOTIENT
	mgm.			*mgm.*	
B_1	0.1	1.0	311	0.025	4.0
Wa-A	0.1	1.0	O	0.0085	8.0
Tebeprotin	0.1	1.0	E_1	0.00408	5.0
V	0.05	2.0	F_6	0.003	20.0
Wa-alc	0.026	2.5			

Primary incubation was $\frac{3}{4}$ hour at 37°C. and second incubation at 37°C. for $\frac{1}{2}$ hour.

2. Precipitation. This method was found to be unreliable in its results, and subject to a considerable personal error in recording the readings. An important obstacle in the general application of the precipitation test is the fact that many of the preparations to be tested cannot be obtained in clear solutions. Suspensions have to be centrifugated and the supernatant fluid must be used for the test; and obviously this fluid does not contain, chemically and biologically, the identical substances as the sediment. In the case of alcoholic extracts, dilution with saline solution is necessary, which yields more or less opaque emulsions. It was frequently noticed that dilutions of 1:1000 produced quantitatively the same precipitate with positive serum as the stock solution. As test serum similarly pooled serum was used as in complement fixation. The test was always performed by layering the antigen upon the serum; readings were taken one and two hours after incubation and twenty-four hours after standing at room temperature.

3. Allergic reactions: For intracutaneous reactions 1 mgm. dry weight in a volume of 0.1 cc. was injected into the skin of tuberculous guinea pigs, which had been infected three to four weeks before the test and which received as a control 1 mgm. of Old Tuberculin intracutaneously. The relatively large amount of 1 mgm. was chosen, because it was expected that some of the substances tested would elicit very weak reactions or none at all.

On account of lack of time and animals, the killing power for tuberculous guinea pigs was determined only for a few representative substances. The Koch procedure was followed.

As to the different derivatives of tubercle bacilli used in this work, no attempt was made to obtain substances of chemical purity; only a rough division into different groups according to solubility was aimed at.

TABLE 2

PREPARATION	NATURE	COMPLEMENT FIXATION		PRECIPITATION	SKIN REACTION AFTER THE INJECTION OF 1 MG.	LETHAL FOR TUBERCULOUS GUINEA PIG, OF 250 GM. WEIGHT	NOT LETHAL FOR TUBERCULOUS GUINEA PIG, OF 250 GM. WEIGHT
		Antigen unit	Anticomplementary unit				
		mgm.				*cc.*	*cc.*
O.T.	Old Tuberculin, P.D. & Co. 0.07122-L.	–	0.50	+	1.5	0.2	0.1
	Residues after extraction with—						
V	Acetone, 20 minutes	0.05	2.00	++	2.0		50
X	Acetone, 5 hours	–	.75	++	1.5		
B_1	Acetone, 50 hours	0.1	1.00	++	1.0		
Q	Alcohol, 30 hours	–	0.75	+	1.0		
G_1	Alcohol and acetone, 20 hours each	–	0	++	1.2		
H_1	Acetone and alcohol, 20 hours each	–	0	++	1.0		
I_{III}	Acetone, alcohol, and ether	–	0.25	+	1.3		
G_3	Acetone, alcohol, ether, and chloroform	–	0.75	++	1.5	50	20
Wassermann-antigen	Tetralin	0.10	1.00	++	1.0		
W-A-E	Tetralin and alcohol		0	+	1.5		
Dreyer	Formalin and acetone	–	0	++	0.5		
Tebeprotin	A soluble protein product, N = 12.3 per cent	0.10	1.00	+	0*		
304	Proteins containing N:14.38 per cent	–	0.50	+	0.8		
308	Proteins containing N:14.99 per cent	–	0.75	++	1.2		20
311	Proteins containing N:14.61 per cent	0.025	4.00	++	1.0	10	5
	Alcohol extracts after extraction with—						
E_1	Acetone	0.00408	5.00	++	0.5		
F_5	Acetone	0.003	20.00	+	0		
O	Acetone, ether, and chloroform	0.0085	8.00	++	0		750
Wa-a	Tetralin	0.026	2.50	+	0.3		
L	Acetone extract after alcohol extraction	–	0	++	1.0		

* Only 0.1 mgm. injected.

This work is being continued at the present time with the pure substances produced by Dr. Johnson. It was possible to include only three of these preparations in the present report. Table 2 shows the results of our work in tabulated form. The conclusion must be drawn that the activity of tubercle-bacillus preparations as antigens in complement fixation and in precipitation does not parallel their tuberculin activity in the tuberculous animal. As far as these comparative studies have progressed to-day, and I may emphasize that we feel that they are far from completion, it appears that the alcohol-soluble substances of the tubercle bacillus are the most active ones in complement fixation (1), and Dr. Long's work (2) indicates that the tuberculin activity is closely associated with substances of the nature of proteins. No statement can be made as yet as to the chemical nature of the substances involved in the precipitation phenomenon. Titration for complement-fixing power was done on seven substances, which Dr. Long isolated from synthetic tubercle-bacillus broth, and which he has tested for their tuberculin activity. In a dose of 0.5 mgm. none of these preparations fixed complement with tuberculosis sera. Dr. Long found that in a dose of 0.1 mgm. two of these preparations gave a one-plus skin test, 4 a two-plus and one a three-plus reaction. Calmette (12) states that the more purified tuberculins are, the less active are they in serological reactions.

Complement fixation and precipitation do not run parallel in tuberculosis, as shown by statistics based on unpublished work by Sweany and Corper. Although the absolute number of positive and negative complement-fixation and precipitation tests on 473 sera is very nearly the same, an agreement of the two reactions is found only in 40.6 per cent of the cases.

Dreyer and Vollum (3) published, in 1924, *A Precipitin Method for the Standardization of Old Tuberculin*. Their test serum was an immune serum produced in a horse after the injection of Dreyer's defatted vaccine. It appears objectionable to use for this purpose an arbitrary immune serum against only one particular group of substances. Dienes and his co-workers (4) have shown that the injection of different chemical substances of the tubercle bacillus into animals will produce immune sera which react only with those partial antigens used in immunization. Dreyer and Vollum tested only Old Tuberculin by their method, and found errors up to 97 per cent of the standard in comparing the results of precipitation with skin tests on human beings. In a series of experiments I tried to duplicate Dreyer and Vollum's results, following closely their

cumbersome technique. Instead of their immune serum, sera from tuberculous patients, which gave a four-plus complement fixation, were used. It was found that Old Tuberculin frequently does not give any precipitate with such sera, and, when precipitates were obtained, their differences in strength with various tuberculin dilutions were never sufficiently clean-cut to allow of a quantitative comparison.

The objections against Dreyer and Vollum's precipitin method may be summarized as follows: An arbitrary immune serum against defatted tubercle bacilli is not acceptable as a standard test object. The method seems to yield uncertain results as applied to Old Tuberculin. The method yields absolutely incorrect results when applied to other bacillary products than Old Tuberculin. The method is not universally applicable to any tubercle-bacillus derivative which may elicit allergic reactions in the tuberculous animal. These statements are further supported by the work of Zinsser and his associates and by Laidlow and Dudley, who separated a fraction from tubercle bacilli which gives specific precipitation with tuberculosis serum but does not elicit any allergic reactions in tuberculous animals. Zinsser and Mueller (5) arrived at the conclusion "that the bacterial extracts representing the antigens for these reactions (allergy and precipitation) are separable, the residue material being particularly concerned in the specific precipitations with immune serum, the so called nucleoprotein being associated with allergic reactions in the tuberculous animals." And, "In the case of bacterial immunization, injection of whole bacteria and the bacterial extracts, as usually employed for this purpose, leads to the formation of antibodies which react in test-tube precipitations with the nonprotein bacterial residues, although these residue fractions are neither capable of inducing antibody formation when injected by themselves, nor, when sufficiently purified, are they capable of inducing reactions in the allergic animal."

Laidlow and Dudley (6) separated a gum-like substance from tubercle bacilli, apparently very similar to Zinsser's residue antigen, which, according to the authors, gives specific precipitation with immune serum up to a dilution of 1:6,400,000, but which does not produce antibodies in animals. They state, "A fairly strong solution gave no response when injected intracutaneously into a tuberculous guinea pig." If these substances were tested by Dreyer and Vollum's method, they would erroneously be considered as highly potent tuberculins.

The relation between complement fixation and tuberculin activity has been discussed by Dienes and his associates (7). Testing different frac-

tions of tubercle-bacillus broth, they found a parallelism between the antigenic activity of their fraction in complement-fixation and the minimal dose eliciting a skin reaction in tuberculous guinea pigs. My own work has been done only on fractions of the bacillus itself and not on broth products. A numerical comparison of Dienes's results shows that, although there exists in general a certain parallelism between complement-binding power and allergic reactions in their preparations, it is not strict, and not by far sufficiently accurate to measure the allergic activity by complement fixation. In previous work Dienes and his coworkers (4) (8) have emphasized the high potency of alcoholic extracts of tubercle bacilli in complement fixation, quite in agreement with our own work. The parallelism stated for broth products does certainly not extend to these bacillary lipoids.

Watson and Heath (9) advocated complement fixation as a method for the standardization of O.T. They claim that the antigenic activity of O.T. in complement fixation accurately parallels its allergic strength. Their work consisted exclusively in comparing various makes of Old Tuberculin. If such comparative studies are extended to other bacillary preparations, as in the work presented here, a striking divergence between the two activities is found. An indirect proof of the unsuitability of standardizing tuberculin by serological methods is given by a study by Čepulič (10) from Much's institution. With three different Old Tuberculins standardized by the Frankfurt method, complement-fixation tests were carried out on the same patients' sera. Some of the representative results are shown in table 3.

TABLE 3

Complement fixation with various Old-Tuberculins, all standerdized with the Frankfurt method according to Čepulič

PATIENT	OLD TUBERCULIN		
	Höchst	Ruete-Enoch	Sächs Serum W
1	++++	++++	++++
2	++++	++++	++
3	++	++	++++
4	0	++++	++++
5	+++	0	+
6	0	++	0
7	0	0	+++

In a recent study on pollen antigens Armstrong (11) arrived at the conclusion that the complement-binding and the allergic activity are not quantitatively related.

On the ground of this evidence it may be said that it is not possible to standardize tuberculins by means of the complement-fixation test.

In the complex relation between humoral reactions and allergy in tuberculosis, the work of the last two decades has well established the fact that these two phenomena are only very loosely connected. Animals will, for example, readily respond to injections of various bacillary extracts with the production of serum antibodies, but they will not show any allergic reaction unless tuberculous tissue be formed in them. Some of the recent work reported here shows that serum reactions and allergy—much more so than in the host—are dependent on dissociable substances in the bacillus. This justifies the broad statement that no humoral reaction can measure the allergic activity of a bacillary product.

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SURGEON-GENERAL CUMMING: Dr. Johnson will give us "The Principles of Bacteriological Chemical Analysis and their Application to the Tubercle Bacillus in Reference to the Large-Scale Production of Tuberculin."

THE PRINCIPLES OF BACTERIOLOGICAL CHEMICAL ANALYSIS AND THEIR APPLICATION TO THE TUBERCLE BACILLUS IN REFERENCE TO THE LARGE-SCALE PRODUCTION OF TUBERCULIN

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In order to lay out a definite plan of analytical technique, which will enable the chemist to determine quantitatively the various constituents of a bacterial cell, it is first necessary to know all the characteristic fundamental constituents which function in the structure of the cell. While we have to-day positive evidence of the existence of many of these cell constituents, such as proteins, fats, carbohydrates, etc., it is true that our knowledge of the actual composition of the bacterial cell is far from complete, and consequently we are unable to make an application of an analytical method which will reveal to us the true composition from a quantitative point of view.

At this time it is quite apparent, and agreed by those who are interested in the development of chemical bacteriology, that a study of the chemical constituents of bacterial cells and of the products of cell metabolism is most important; but as long as the condition prevails, that we have no thorough and severely tested method of analysis, it will be impossible for the chemist to make any advance in this field, and we will remain in that state of chaos and chemical ignorance that prevails at the present time.

An accurate knowledge of cell constitution will never be obtained and the presence of hidden combinations revealed, until analytical methods are adopted which are based on an accurate understanding of the distribution of fundamental elements functioning in the constituents of the cell. In order to obtain data which will enable the chemist to establish and adopt a practical analytical technique, we must follow the distribution in the cell of the three elements, nitrogen, phosphorus and sulphur. A knowledge of the distribution of nitrogen is absolutely essential as a guide-post to reveal hidden combinations containing this element, and in the case of phosphorus we are dealing with an element which is always associated with organic structures characteristic of phosphatides and nucleic acids. According to new biological data which have been presented in recent years, it is very important to follow in bacterial analysis the distribution of sulphur. Oxidation and reduction changes in cell

life are undoubtedly influenced by the presence of organic combinations containing this element. Whether sulphur actually functions in the metabolic changes of the tubercle-bacillus cell remains to be established.

In order to produce data of any value leading to an accurate knowledge of the composition of cells, both qualitatively and quantitatively, it will be necessary to consider also very carefully several influencing factors; otherwise, the data obtained by analysis will be of no practical value, and will consequently represent so much wasted time and thought.

In the light of the rapid alterations which cells can undergo, due to the influence of enzymes capable of stimulating autolytic changes, it is necessary that every chemist, who undertakes chemical research in this field, have some knowledge of the nature of the biological conditions influencing and altering the composition of the cell.

In the first place, we must consider carefully the question of conditions influencing the growth of the bacteria. It is very important that the purity of the necessary reagents composing our synthetic media be accurately known, and that the media be of uniform composition in all work; otherwise, metabolic changes may be introduced in cell growth, which will lead to constitutional changes that cannot be revealed by any analytical procedure under our control. Again, after final growth and maturity of the cell it is very important that the bacteria to be studied be carefully separated and washed free from the culture media, so that such contamination will not introduce errors into our analytical results.

Our experience in the Yale laboratories with tubercle bacilli has already taught us that it is very necessary to know under what conditions the death of a cell is brought about, before one proceeds to apply his analytical procedure. The data obtained by analysis of a tubercle-bacillus cell killed by chemical treatment at temperatures below 37°C. will not be in agreement with data obtained by analysis of cells killed by heating at or above 100°C. Especially is this true if one proposes to determine, for example, the actual content of water-soluble protein. We now know that a water-soluble protein fraction, which can be extracted from cells that have not been autoclaved, is rendered absolutely insoluble by coagulation if the fresh cells are first heated above 100°. This is a very important fact, and one which must always be considered in the development of any method to be utilized in manufacturing an active tuberculin preparation from the tubercle-bacillus cell.

From what we have been able to learn from our analytical experience with desiccated tubercle bacilli, it is apparently necessary to free cells

from fat before proceeding with the application of later analytical procedures. Here again we are dealing with a technique which must be carefully controlled, or alterations in composition will be introduced which will decidedly affect our analytical results. In those cases in which we are dealing with a mixture of fatty acids, fats and waxes spread throughout the structure of the cell, it is a matter of considerable importance to know, before selecting an inert solvent for extraction purposes, whether it boils at 35° or 100°. Whether some modification of fat enters into the structure and composition of all bacterial cells has not been established, but it is true that in the case of the tubercle bacillus this organic constituent is a very important one and somewhat troublesome from an analytical point of view.

One of the most difficult and important problems that confronts us in our analytical work to-day on the tubercle bacillus is that of interference of the fat and waxes with the extraction and separation of the protein principles of the cell. This question will probably present itself in every future analytical research dealing with a determination of the composition of bacterial cells. In tubercle bacilli these fatty constituents represent a very large proportion of the cell and offer a resistance against the invasion of water into the cell structure. They are powerful obstacles to chemical extraction. It is necessary to overcome this by removal of this fatty constituent without alteration of the character of the protein principles functioning in the cell. In order to accomplish this we must proceed under conditions that will not lead to coagulation of albumen. In order to overcome this barrier we have adopted the principle in our work of "ether plasmolysis," which was applied so successfully by Chibnall in the case of plant cells from alfalfa and spinach. Treatment of desiccated tubercle bacilli for prolonged periods at ordinary temperatures with ether serves not only to remove all ether-soluble fat and free fatty acids, but the treatment also alters the nature of the protective membrane entering into the structure of the cell, and thereby favors the penetration of water. This procedure leads to the practical result that by cold-water extraction after ether plasmolysis a water-soluble protein can be separated representing about 6 per cent of the original weight of the desiccated cell. If, however, the tubercle-bacilli cells are autoclaved before *ether plasmolysis*, practically no water-soluble protein can be extracted. From the preliminary reports which have been submitted to us by workers in the biological field it is quite apparent that this particular protein fraction is the most potent tuberculin preparation that

we have thus far succeeded in separating from the desiccated cell. In other words, we must operate at low temperatures and if we change our technique by removing fats and waxes, for example, by digesting with boiling toluene, or boiling alcohol, we alter the character of certain active protein constituents, thereby making them insoluble in water and weakening their potency as tuberculin preparations.

Before we are in any position to discuss quantity production of tuberculin preparations from desiccated tubercle bacilli it is absolutely necessary to ascertain the relative value of the different protein fractions separated under the conditions of analytical procedure adopted. As I have stated above, it is possible to separate by cold-water extraction a protein fraction equivalent to 6 per cent of the weight of the dry cell. Doctor Long reports for this protein a very high tuberculin activity. If, therefore, we decided to adopt this fraction as our tuberculin preparation, and disregard the remainder of our cell, we would have a basis of calculating the cost of a definite product of commercial value. But other considerations enter in here, which must be taken into account. We find that the fraction remaining behind after removal of this water-soluble protein fraction still retains strong tuberculin activity, but much less than that of the fraction soluble in cold water. This protein, insoluble in cold water, can be extracted with dilute alkali and purified by precipitation with acids, and it still retains a very pronounced potency as a tuberculin preparation. Are we to throw this fraction away as useless material, or are we to appropriate it in our adoption of a standard tuberculin unit? It is very important, in the light of these results, to come to a very definite conclusion as to what shall constitute a standard tuberculin unit. Will we adopt one more active than that represented by our first water-soluble fraction, or will we choose a weaker unit, and by dilution utilize a large part of the cell protein, which under the first experiment will be thrown away? In other words, in my opinion, all of these questions must be very carefully considered before we can come to a definite or final conclusion regarding any recommendation for standardization of our manufactured product. If we can conserve, in any way, active material of the cell which, according to present practice, is now thrown away in the process of manufacture, it is very important that we do so. It is undoubtedly true that we have before us the possibility of developing and utilizing a larger proportion of our desiccated tubercle-bacillus cell than has hitherto been possible by present-day methods of commercial manufacture.

In all work dealing with the preparation of protein principles from bacterial cells it will be necessary hereafter to consider very carefully the question of the action of alkali on these products. The protein tuberculin fractions are very sensitive to the action of alkali, and protein extracts which are very potent as tuberculins are weakened in their activity by alkali treatment. What change takes place in the protein molecule by the action of alkali, it is difficult to say at this date, but it is very probably associated with an alteration in the amide or polypeptide structure of the protein molecule.

In the carrying out of a line of research, such as is represented by our investigation of the chemistry of the tubercle bacillus, and directed toward a search for that respective fraction which will exhibit the highest tuberculin activity, it is necessary that the chemist have the closest coöperation of workers trained in certain fields of biological research. The development of any method for the separation and purification of an active tuberculin fraction cannot be accomplished successfully without the assistance of experts who are competent to give accurate reports regarding allergic, serological and cytological reactions of the various fractions which we succeed in separating. Unless such tests are made for us during the actual course of our chemical investigation, we are severely handicapped in the progress of our work, and no means is available whereby we can decide whether we are working in the right direction. It is necessary to have beacon lights to properly steer us in our course, otherwise we are liable to waste valuable time in unprofitable work.

In our researches during the past two years we have had the good fortune of having associated with us in the direction of our joint research, Dr. White, who has perfected an organization which has served to promote successfully the preliminary development of our major problem. We are fortunate in having his hearty coöperation and interest. The preliminary tests on allergic reactions which have been made for us by Dr. Long have been extremely helpful, and have served many times to steer us along the road which has led to progress in our work. We have been awaiting the reports of Dr. Pinner and Dr. Cunningham with very much interest. There is no doubt in my mind that the continuation of our plan of close coöperation is bound to lead to the discovery of new facts and the contribution of valuable data which will aid in the solution of the tuberculin question.

GENERAL DISCUSSION

SURGEON-GENERAL CUMMING: Dr. Smith, will you open the general discussion on these papers?

DR. SMITH: The question of tuberculin is evidently an important question, judging from the papers to which we have listened to-day. My personal experience rests with the old Koch period when we worked with Old Tuberculin. In the years preceding 1913 I spent a great deal of time on this subject from the serological point of view, but much of the work was never published because it never reached any stage of completion.

There are still a good many questions in my mind which make me wonder whether the study of the ordinary tuberculin has been carried to a satisfactory point as a preliminary for this work, and I was very much interested in what Dr. Johnson said about the difference between the boiled tubercle bacillus and that treated in the cold. I remember distinctly the great allergic reactions produced by the ordinary filtrates and the cultures in those years, but I remember that the cold filtrate was much stronger than the boiled. I remember distinctly tuberculin reactions in which 0.1 cc. would prove fatal to a tuberculous guinea pig. I know some tuberculins would be only one-third of this strength.

Now, it seems to me that we have not entirely exhausted that preliminary study which will enable the chemist to know what is the most satisfactory substance for him to work with,—what are the actual chemical foundations of tuberculin. It seems to me that the aim of all those who are working with tuberculin is to determine what that substance is. We have just listened to Dr. Pinner's paper, in which he showed that there is a distinct difference between the complement-fixation, precipitin and allergic fractions. What we want is knowledge of the allergic fraction; this is what we depend upon. We know the allergic reaction is a safe one on which to base a diagnosis in a very high percentage of tuberculous animals—at least in 95 to 99 per cent. It is of extreme interest to know that serological tests are not of themselves adequate and we must, after all, get back to the live tissue of the animal body in order to get that reaction which will be most useful in practical application to man and animals. There are a great many unexplained questions in these fields, which, I presume, will be summarized by those in charge of this work.

There is one question I wanted to ask: Has any one made a study be-

tween the very old prolonged cultures which have been growing for many years and those which have been isolated relatively recently as regards lipoids? It seems to me that is something the biologists could do for the chemists, to show the difference between the 20-year-old cultures and the 18-month-old cultures and the lipoid ingredients. Possibly this has been done and is on record.

SURGEON-GENERAL CUMMING: Dr. Krause, will you continue the general discussion?

DR. KRAUSE: What we have heard here to-day confirms much work that has been done in the past. Personally, I cannot see any other approach to the standardization of tuberculin than the one that stands out prominently in these papers, that is, the application of the allergic reactions. Most past work has shown pretty definitely that it is the protein fraction that elicits the allergic reactions, but I also think that if lipin were added to the protein one should get much stronger reactions. For this reason I was wondering whether, if Dr. Pinner had added a little lipin to the fraction which he got from Dr. Johnson, the action of his antigen would not have been enhanced. This might very easily be studied along the lines of Dr. Pinner's work.

I was greatly impressed by the general trend of Dr. Long's remarks, and I wondered whether animals might not vary in giving testicular reactions as they do in their skin reactions. I should like to hear this discussed a little more in detail. In using the allergic reactions as a method of standardization I agree thoroughly with what Dr. Schroeder has said, that "tuberculin will stand a tremendous amount of manhandling." It is certainly true that complement fixation and other serological methods do not offer any hope in regard to the standardization of tuberculin, because, as Dr. Long said, we understand by tuberculin only a something which gives a definite effect, and it seems to me that we must work on that effect, that is, the allergic response to the tuberculin, if we are going to standardize tuberculin.

SURGEON-GENERAL CUMMING: Dr. Hektoen, will you continue the general discussion?

DR. HEKTOEN: I have nothing to say in addition to what has been said by previous speakers, but I should like to voice the impression I have obtained from what has been said, namely, that it seems to me the stage is clearly set for continued active coöperative work between these

workers and the different scientists on these questions concerning tuberculin and its standardization. I cannot say anything in the way of definite details, but the impression is made very strongly that this work should be continued.

SURGEON-GENERAL CUMMING: Dr. Lewis, will you continue the general discussion?

DR. LEWIS: It seems to be generally agreed here that the complement fixation and precipitation reactions are not adequate for the determination of tuberculin potency. The two reactions first mentioned may perhaps be closely interrelated, but they certainly rest on a different basis than the allergic reaction, when the chemical nature of the respective antigens is considered, and cannot be taken to represent it actually in however many cases the relative potencies may roughly coincide, and it is well that we seem to be able to reach this conclusion.

Until a few months ago at least, tubercle bacilli were frequently spoken of as "defatted" when they had merely been kept for some time in cold alcohol. To speak of the bacilli as "defatted," if by that we are to understand that the fats and lipoids have been completely removed, is absurd when such a limited extraction has been used, and is of difficult and uncertain accomplishment when even the most vigorous and thorough extraction methods are employed. The term has been so loosely used so long that it would seem advantageous to eliminate it entirely. Certainly no work to-day can be regarded as informing unless the exact extractive measures used are described and their results stated in terms of the amount of extractive still retained by the residue.

With regard to intracutaneous methods of testing the potency of tuberculin on guinea pigs, I should like to remark that Roemer is responsible for the idea that such a method could be worked out. We have never considered that our work (Lewis and Aronson) furnished a complete background for a system of testing, but thought when it was done, and I still think, that the interest in the idea should be kept alive.

In this connection I should like to inquire of those present who have the duty of producing and testing tuberculin whether there are essential difficulties in the practice of the older methods, and, if so, what these may be. Is there really difficulty in determining the potency of a recent preparation compared to one kept in the laboratory as a provisional standard? Is there real difficulty in turning out a product which will compare favorably in potency with an acceptable standard? From the

standpoint of the experimental laboratory it has apparently been assumed for many years that these processes could be carried out in practice with relative ease and certainty. Is this assumption justified?

I would only say further that if it were considered desirable to substitute an intracutaneous for a subcutaneous tuberculin test as either a provisional or final step in determining tuberculin potency, we should not limit our vision to the guinea pig. An animal such as the calf, presenting a much less limited skin area, might prove more useful in practice.

SURGEON-GENERAL CUMMING: Dr. Williams, will you go on with the general discussion?

DR. WILLIAMS: On the scientific discussion, I do not feel able to comment at all, but I should like to say that it is a source of great satisfaction to me and to the National Tuberculosis Association to have an opportunity to see the close coöperation that is being carried on in this work between the Bureau of Animal Industry and your own Bureau; I feel that the correct thing is to seek further knowledge in this field, and I am particularly glad to have heard Dr. Hektoen's statement in regard to the coöperation between the different workers who are carrying on research in coöperation with the National Tuberculosis Association. Three or four years ago I felt that it might be very difficult to get that coöperative effort, but we seem to have been able to obtain it through the Research Committee, and perhaps that Committee has been more or less instrumental in bringing about the coöperation between the three different institutions here to-day. I think you know, Dr. Cumming, that I have always been much interested in the relation between voluntary and official agencies, and have tried to see that the official agency had and kept its proper place, and we want to keep our proper place and not overstep on the ground of the Federal agencies. It is this very efficient cooperation which I am delighted to witness.

SURGEON-GENERAL CUMMING: Dr. Dorset, will you close the general discussion?

DR. DORSET: The standardization of tuberculin differs for human and bovine practice. The extreme accuracy required for the former is not quite so necessary for the latter. At the same time, tuberculins now on the market in bovine practice vary considerably: some are superpotent and some are so weak as to be useless. Even the product of one manufacturer may be superpotent one year and the next year almost

devoid of potency. It is difficult to explain these occurrences, but I have thought it is because manufacturers do not give proper attention to the essential factors in production. If something could be done in the way of standardization of production it would help to provide a standardized product for veterinary purposes.

We do not test every batch of tuberculin that we produce, but we have standardized our methods, and we insist that they be always uniform. Now, what has been the result? This tuberculin of ours, while probably not so potent as may be found on the market at times, according to the results of Dr. Schroeder's tests over a period of a good many years, tested out a good many times a year, runs very uniform on guinea pigs: it will kill a tuberculous guinea pig with a certain dose, and we can expect it to do that every time. Therefore, we feel that we have a sufficiently standardized tuberculin for veterinary use; and this has been accomplished by standardized methods of production. Thus, I am interested in the second question that was submitted, that is, the control of standardization and methods of production.

I think you may all easily see, by looking at these compilations which Dr. White has prepared from the data secured from 13 manufacturing firms, that there is a wide variation in the methods of production in commercial practice. We have found that our mass of bacilli after filtering is 0.5 gm. per litre. I have thought sometimes of using this as a criterion of the amount of tuberculin that should be produced. As to the strains of bacillus, ours came from Doctor Trudeau about 1891. We have the same culture growing in our laboratory now. Dr. Schroeder got his from Saranac Lake about 1891. I have recently been injecting a series of animals with some tuberculins from the market, comparing them with our regular tuberculin.

(The meeting adjourned for luncheon at 12:45 P.M.)

SPECIFIC DISCUSSION

Afternoon Session

SURGEON-GENERAL CUMMING: Dr. White, will you comment on the analysis of the League of Nations questionnaire?

DR. WHITE: There is before each one of you a copy of the questionnaire that was sent by the Health Section of the League of Nations to the

Surgeon-General of the U. S. Public Health Service, to distribute among the different manufacturers of tuberculin in the United States and a synopsis of the answers to this.

It will be apparent from the answers to this questionnaire:

First, that the United States Bureau of Animal Industry produces a large part of the tuberculin used in the United States, that is, 15,974,500 doses as against 7,100,540 doses. Thus the Bureau of Animal Industry produces nearly three times as much tuberculin wholly for animal diagnosis as all other manufacturers combined.

There has been a steady increase in the production of tuberculin for human use in the past three years and an increase in that used for diagnosis in pigs and chickens, coincident with the apparent increase of tuberculosis among these animals.

Second, there is no uniformity as to culture medium, strain of microorganism, period of growth, after-treatment, that is, sterilization, filtration, dilution, or use of preservative.

Third, in only two States is there a law covering standardization.

Fourth, when tests of strength are made there is no uniform method of infecting the guinea pigs used, nor of determining the infecting dose which they receive.

Altogether, the procedure in manufacture is variable, and much can be gained by uniform practice. As Dr. Dorset has shown, a uniform practice in production yields a very uniform strength of tuberculin year after year.

The two Bureaus responsible for licensing the manufacture of tuberculin are a part of this Conference, and I am sure manufacturers will welcome any suggestions from them which will improve their product.

Suggestions as to strain of microörganism, medium, size of flask, surface area to bulk of medium, time of growth, weight of growth, after-treatment, preservative, dilution, and testing of strength would mean great improvement, even though the bulk of production is largely confined to one laboratory.

I think now, sir, with this material and the morning papers the Conference may proceed to a discussion of the individual questions.

SURGEON-GENERAL CUMMING: We have offered for your discussion three questions:

First, have we sufficient knowledge at the present time to warrant the establishment of a standard for this substance?

Second, Can we, with our present knowledge, make important improvements in the present methods of manufacture of tuberculin, and what should these improvements be?

Third, What lines of study are the best for us to pursue to enable us to arrive at a better standard of tuberculin?

We will now present the first question.

DR. SMITH: In order to bring the question before the conference I make the following motion:

We have not at present sufficient information to recommend definite changes in the standardization and testing of tuberculin as now practised by different countries, nor shall we have until the different methods proposed have been exhaustively studied comparatively.

DR. HEKTOEN: I will second this motion.

SURGEON-GENERAL CUMMING: The motion is now before you for discussion.

DR. DORSET: As I understand the motion, there is not sufficient knowledge available to us at the present time to warrant the adoption of an international standard; because we do, I think, find it necessary to have some sort of test for tuberculin, some method that we call "standardization," but which is not exact enough to warrant its establishment as an international guide. But we need some sort of guide. I am sure that the Conference does not intend to take the position that there is no means by which the relative potency of tuberculins can be determined at the present time, or to take the position that such a thing could not be done in a rough way. But we should not make this international.

DR. SMITH: The motion is intended to imply that we are not prepared to disturb the present methods.

Before we have a decision may we have a statement as to present methods from Dr. Dorset? We probably all know them, but it might be well for Dr. Dorset to state them as practised by the Bureau of Animal Industry in this country.

DR. DORSET: As far as our own practice is concerned, we do not test the potency of each batch of tuberculin as it is prepared. We specify the method of production, and batches are tested at intervals. Dr. Schroeder tests these by the guinea-pig killing test; that is, their lethal doses for tuberculous guinea pigs are determined. This is really our method of standardization. The requirements for preparation are rigid and are more constant than the actual testing of the product after it has been prepared.

DR. STIMSON: We might divide the question into (1) standardization of bovine tuberculin which each State would determine for itself, prescribing the methods to be used in preparation with occasional control tests, and (2) the necessity for further comparative study to enable us to standardize human tuberculin with accuracy. Would that make our position clearer to those who do not hear the discussion but read the conclusions only?

DR. LONG: It might be well if in some way this idea could be conveyed. Comparison of methods is necessary. Five or six methods have been proposed by various people, and to settle upon any one of these without a comparison would undoubtedly lead to error. There has been no adequate comparison, and there is no reason for upsetting present practice until this is done. Picking out one method without comparing it is not exact.

Supposing that an international standard were adopted by the League of Nations Committee, how far would that have weight or force? Would it be merely a focal point about which methods would eventually be expected to crystallize, or would it have weight in many places even though it did not have here?

SURGEON-GENERAL CUMMING: I think it would have a good deal of weight in European countries and in South America. In England they are going through the throes of standardization, are they not, Dr. White?

DR. WHITE: They are having the same discussion in England that we are having here. The Medical Research Council has just published a report of their results and comparative tests of tuberculin in cattle (*Special Report Series No. 94*). Among the questions facing the English committee was one, "Can the present methods of standardizing tuberculin be improved?" A method of standardizing Old Tuberculin by a precipitin method is offered by Professor Dreyer and Mr. Vollum, but, as you have seen, when using pure fractions there is no definite relation between the precipitin fraction of the bacillus and the allergic fraction. So far as the testing of cattle allergy is concerned, the English committee recommends a double intracutaneous injection in the same skin area of the neck of the animal to be tested.

In Canada Doctor Watson and Doctor Heath suggest a complement-fixation method, which runs roughly parallel with Doctor Schroeder's tests. But here again it would seem that allergy fractions and antigenic fractions for complement fixation of the tubercle bacillus are not the same.

This Conference, therefore, must look toward a plan for separating these

different fractions, and isolating the allergic fraction in stable form which can be readily diluted as the first step in standardizing tuberculin.

DR. SCHROEDER: I sent Doctor Watson a dozen or so samples of tuberculin I had tested. These he tested by the complement-fixation method and reported results to me. While the results he obtained were not like mine they were sufficiently like mine by the reading that, if I had based reactions on these tests instead of on my own, they would have been practically the same.

SURGEON-GENERAL CUMMING: The question now before us, moved by Dr. Smith and seconded by Dr. Hektoen, is, "We have not at present sufficient information to recommend definite changes in the standardization and testing of tuberculin, as now practised by different countries, nor shall we have until the different methods proposed have been exhaustively studied comparatively."

The Conference unanimously adopted this resolution.

SURGEON-GENERAL CUMMING: We now come to the second question, "Can we, with our present knowledge, make important improvements in the present methods of manufacture of tuberculin and, if so, what should these improvements be?"

DR. WHITE: In presenting that question it will be clear, by referring to the answers to the questionnaire, how enormous is the production of the Bureau of Animal Industry as compared with all the rest of the United States. There are only two States that have a law covering any test of tuberculin, and neither the Bureau of Animal Industry nor the Public Health Service has suggested, up to the present time, to the different manufacturers how they should proceed, save when they have asked for advice.

DR. DORSET: The Bureau of Animal Industry has made certain requirements of producers of tuberculin. For example, we have required that their culture media shall be placed in containers, so that the surface area of the medium in the container shall bear a certain relation to the total volume of culture fluid. I forget the exact requirements, but I think it is about 8 square inches of surface to 100 cc. of broth, and the manufacturers are required to put their medium in containers in this proportion. We found one commercial producer making tuberculin in large flasks holding about 3000 cc., with a surface area equivalent to about 100 cc. of broth, in other words a tremendous amount of culture fluid and very minute surface area. And the tuberculin from this ap-

parently led to some disastrous results in some herds on which it was used.

The amount of growth to the total amount of culture fluid must be taken into account, and we require this also. I do not believe that we can go any further, except to say that true bacilli must be used. We require that cultures be submitted to our laboratories, and they are always examined before a license is issued.

DR. WHITE: It seems to me that the Bureau of Animal Industry and the Public Health Service should have standards of methods for all producers of tuberculin.

DR. DORSET: Probably one thing that has prevented this is the feeling that perhaps others could make as good tuberculin as ours by different methods. But the nearer we can reach a standardization the better.

DR. STIMSON: If the Bureau of Animal Industry does not control absolutely the tuberculin for bovine use the Public Health Service does still less in the way of applying anything like standardized methods for the production of tuberculins or substances which would have to be handled under that term for human use. These substances are produced by so many different methods, some of them growing the tubercle bacilli on all sorts of media and handled in all sorts of ways, that we cannot possibly get at a method which would cover them all, unless we arbitrarily make a standard for the production of therapeutic tuberculin for human use, and refuse to license any other kind. That would put us in a position of depriving the medical profession of preparations which they believe to be of use. If we believed the preparations they want are no good, and had good reason to back up our belief, we could do it. Considerations like this are what led me to suggest in the beginning that we might have to split this whole question into tuberculin used for diagnosis of tuberculosis in cattle and tuberculin, or substances which would have to be included under the generic term of *tuberculin*, to be used for diagnostic and therapeutic use in human beings. Dr. McCoy is more familiar with the details of the administration of the Biological Act, as it refers to tuberculin, and I should like to hear what he thinks about the possiblity of standardizing tuberculins for human use.

DR. MCCOY: I have very little to add to what Dr. Stimson has said. One of the reasons why we never pressed the matter of standardization at the Hygienic Laboratory, in addition to the reasons given by Dr. Stimson, is the very fact that 99 per cent of all tuberculin that is produced

is used for diagnostic purposes and comparatively little for treatment. Our law covers only prevention and treatment. It does not cover diagnostic agents.

We have had so many other matters that appeared to us more pressing problems of standardization, and to afford better prospects of solution, that we have ignored tuberculin. I do not recall, however, a meeting of our Advisory Board when the matter has not come up.

DR. WHITE: You have no jurisdiction in diagnostic uses?

DR. MCCOY: No. The law covers only prevention and treatment. If there appeared to be a reliable and satisfactory method of standardization we could of course enforce it but, as Dr. Stimson said, there are so many tuberculins actually in use to meet the preferences of individual groups of physicians that standardization seems extremely difficult.

DR. DORSET: The law that the Bureau of Animal Industry works under is worded almost identically with yours. It applies to any virus, serum, toxin or analogous product used for the treatment of domestic animals. If your interpretation of the word "treatment" is correct, I suppose we have been exercising illegal control over the production of tuberculin for use in cattle. We felt that the word "treatment" meant *use* on the animal, not necessarily therapeutic use, and we have so considered it.

DR. MCCOY: Our law reads for the prevention and cure of diseases in man.

DR. SMITH: Should you not argue that diagnosis is a necessary preliminary to prevention and treatment?

DR. MCCOY: We have stretched it a little, and manufacturers have asked that we stretch it to cover such a diagnostic agent as that used in the Schick test, which is also used as preliminary to active immunization. The producers are always anxious that we protect them.

DR. SMITH: Can you treat without diagnosis?

DR. MCCOY: I feel, that with our influence with the producing houses we would have no difficulty if we were to attempt to establish a standardized tuberculin. We have had a decision on the scope of the law as applied only to prevention and treatment, not to diagnosis. If it is applied to diagnostic agents, it would lead us very far afield, and I do not know how we would control it.

DR. SMITH: It seems clear that the strength of tuberculin should be the same throughout the United States. When tuberculosis has become less and less there will be growing up a susceptible stock, and there must

be a diagnostic agent which is above criticism. Because of the growing importance of tuberculin in diagnosis in disclosing tuberculosis as a disappearing disease it becomes a question of economics, and we must take cognizance of it.

DR. WHITE: There will undoubtedly arise within a year or two the question of production of tuberculin on synthetic media. Already, under Dr. Dorset and the Research Committee, work has progressed very rapidly. It seems fairly certain that the tuberculin substance of the tubercle bacillus should be extracted in the cold; that heat coagulates a large part of the active substance which is then precipitated; that the bacillus contains a very large fraction easily extractable which is now wasted.

These considerations, if proved, justify the action taken on the first question of the day, but as they are not yet exact enough for practical use a definite prescription for the manufacture of Old Tuberculin, following the practice of the Bureau of Animal Industry, would be very welcome and would form a base-line from which future uniformity would naturally follow as knowledge grows.

DR. DORSET: The term "tuberculin" is so broad that you cannot possibly get a set of regulations to cover tuberculin in general, but I believe that the term "Koch's Old Tuberculin" means a fairly definite thing. It means the microörganism cultured on a meat broth with peptone added. I do not know whether or not you could restrict that to the human type of bacillus. I do not remember whether Koch used veal broth or beef broth, but Koch's Old Tuberculin is the chief tuberculin used, and if that were defined it would leave everybody free to prepare other tuberculins but they could not use the name, "Koch's Old Tuberculin," without conforming to certain specifications. If it were decided by an authoritative body that Koch's Old Tuberculin meant a certain thing we could see that that was used.

We have not felt that we should restrict the methods that are used in producing tuberculin. We have been using experimentally some forty or fifty thousand doses of synthetic tuberculin. In preliminary tests this appears to be superior to that which we have been getting from broth cultures. If we had been restricted only to broth cultures, then we might have excluded the synthetic work, which might have stood in the way of improvements in the industry.

The nearer we can reach a standardization the better. I am glad to

hear Dr. Smith's suggestion. We have gone about as far as we dared go. If we ought to go further I am sure we should like to.

DR. SMITH: Wouldn't the synthetic tuberculin be cheaper?

DR. DORSET: It will not be more expensive. Although asparagine is very expensive and would cost above what is spent for meat, I believe there would be considerable saving of labor, and we might be able to produce it cheaper.

DR. SMITH: Are you likely to find that there are certain reactions that are absent in the synthetic medium?

DR. DORSET: We expected that we would do away with certain reactions, but instead of that we have more positive reactions from the synthetic cultures than from the broth cultures, thereby indicating that there was nothing in the broth that was causing an undue number of reactions. The difference between the two appears to be that the synthetic tuberculin reacts when the ordinary broth tuberculin does not, and we do not know just why that is.

The method of growth on the two media is different. On broth, the pH reaction of the medium with human bacilli rises and then falls quite sharply. On the synthetic medium we do not get this curve: it rises sharply, and continues on a plane similar to that of the bovine bacillus. I do not think we should say that cultures three or four weeks old are old enough to produce tuberculin. The period of standing may be an advantage. With the synthetic medium the growth continues apparently over a much longer period of time.

DR. LEWIS: I would propose the following motion:

The Commission believes that a test based upon the following definitions will aid in bringing about a uniformity in practice:

Tuberculin (O.T.) should be defined as a product derived from bouillon cultures of the tubercle bacillus (human type) by filtration and concentration, and should have the following essential characteristics:

a. It should cause typical symptoms of allergy (constitutional or skin reactions) in tuberculous animals and at the same time be without effect on normal animals.

b. Its potency should be sufficient to cause the death of tuberculous guinea pigs within 24 hours after intraperitoneal injection of 0.25-gm. doses per 500 grams of guinea-pig weight.

In practice the strength of other forms of tuberculin should be computed in terms of O. T. (Old Tuberculin).

Tuberculin from bovine strains of tubercle bacilli should conform to the standard for O. T. (Old Tuberculin).

Tuberculins from avian strains of tubercle bacilli do not conform to this standard for O. T., and should be considered independently.

It is desirable for Government Bureaus concerned with licensing tuberculin to issue a statement of a method with which a product of suitable potency and purity is more or less uniformly obtainable.

DR. DORSET: I second the motion.

SURGEON-GENERAL CUMMING: You have heard the motion: what is your pleasure?

DR. SMITH: Before voting I should like to ask if there are any data to determine whether abundant growth of bacilli means greater quantity of tuberculin and whether more tuberculin is derived from bacilli from cultures of, say, 18 to 20 years, than from recent cultures of, say, 1 to 2 years, on artificial media?

DR. DORSET: I think that with a given culture the amount of growth is a pretty good index of the tuberculin produced. The tuberculin arises only from the growth of the bacilli. The more bacilli, the more of the active substance that is extracted by the culture medium up to the limit of solubility. If we could control tuberculin, one of the first steps would be to require a certain weight of tubercle bacilli per gram of Koch's Old Tuberculin.

On the second question I have no data.

I would not propose that weight alone be a guide. Even though it is true that the tubercle bacilli are extracted slowly, that could be taken care of by prescribing a certain period which the cultures must remain in the incubators, and when the product is finished and the bacilli filtered off there must be a certain weight of bacilli as representing a certain amount of tuberculin.

DR. LONG: Would that not be an important point to add to your specifications, that a certain amount of time be allowed to elapse before maturity is reached?

DR. DORSET: One culture may be inoculated and grow only half as rapidly. The one growing more rapidly and producing more material, if left in the incubator the same length of time as the other, would have the greater strength.

DR. PINNER: Is there any evidence that uniformity of production would ensure a uniformity of potency? If we had uniform directions for production we would not be any more sure of potency.

DR. DORSET: To reply to Dr. Pinner, I understand him to ask whether

there is any evidence that uniformity in methods of production will necessarily bring about uniformity of potency. I think I referred this morning to the fact that we had had uniform methods of production for a long time with our product, and that it had been submitted to repeated tests by Dr. Schroeder, and that it has always shown a remarkable uniformity in potency, therefore indicating that uniform methods of production do result in producing a tuberculin of uniform potency.

DR. PINNER: Were the strains uniform?

DR. DORSET: Yes, had we changed our strains we would have had different results, but I take it that uniformity of methods of production includes uniformity of strains of tubercle bacilli used for the purpose proposed.

DR. KRAUSE: What about foreign tuberculins?

DR. WHITE: Foreign tuberculins are more easily handled under the same jurisdiction. If the methods of preparation were uniform, it would wipe out a good many of the gross differences that exist to-day and would regulate foreign tuberculins in the same way as domestic. Biological products crossing Federal or State borders are much easier to control than those within State lines.

DR. MCCOY: The restrictions are the same. So far as human tuberculins are concerned the question is merely academic. We do not have two importations a year of foreign biological products. If we decided that it was wise to prescribe that a certain human tubercle-bacillus culture be used, we could insist on the foreign firms doing the same as the American. How to detect infraction of the regulation is a more difficult question. Unless it becomes an article of interstate commerce we have no control.

SURGEON-GENERAL CUMMING: Are you ready for the question?

On vote the resolution proposed by Dr. Lewis, seconded by Dr. Dorset, was unanimously adopted.

SURGEON-GENERAL CUMMING: The third question before you is, "What lines of study are the best to enable us to arrive at a better standardization of tuberculin?" Dr. White, will you outline the present plan of study?

DR. WHITE: The present plan of study is one of coöperation between the Hygienic Laboratory of the United States Public Health Service, the Bureau of Animal Industry of the Department of Agriculture, the Research Committee of the National Tuberculosis Association, and the

University research laboratories. The Chairman of the Research Committee is in charge of the division of tuberculosis research in the Hygienic Laboratory, thus making a government Bureau the clearing house for the knowledge accruing from the different researches.

The part of the work directly bearing on the subject of tuberculin is carried on as follows:

Large quantities of tubercle bacilli have been prepared on a synthetic medium, as follows:

Formula

All ingredients for this whole work were purchased at one time and were of known composition. This was true also of the glassware. Parke, Davis & Co. and H. K. Mulford & Co. have coöperated in doing all the work of growing the bacilli. When each crop is ready it is carefully filtered; the filtrate is sent to Dr. Long for analysis, and the bacilli, air-dried, are sent to Dr. Johnson of Yale.

A careful plan of chemical fractionation is followed on both of these primary divisions of the growth of the bacillus. The bacilli are presumably in large measure living at the beginning of this work. As each fraction is separated, it is sent to the Chairman of the Research Committee, and by him distributed to different laboratories for serological, cytological, and allergic studies. The results of these studies are brought together from time to time in conference, and the knowledge correlated, and the next steps in analysis decided upon. The different workers are not familiar with the steps pursued by the chemists, so that they are not influenced in their interpretation by a knowledge of the substance with which they are dealing.

The conferences for correlation are held before a small jury of experts carefully chosen for criticism and advice. Already it is quite clear that different fractions are concerned with different phenomena, and it seems promising that this group action will rapidly advance our knowledge, so that soon we may be able accurately to deal with this problem. The chance for field study of fractions is opened by the coöperation of the Bureau of Animal Industry.

This is only one of the departments of the work of the Committee. The others deal with the anatomy of the lungs, the biology of the tubercle bacillus, the cytology of animals suffering from infection with tuberculosis, the development of fibrous tissue, and the relation of primary to

secondary infections. While the details of these studies do not belong here, they are all of help in putting together the puzzle of this disease.

I shall be glad to answer any questions.

DR. DORSET: I move that

This Commission approves the present coöperative plan of research being carried on by the Research Committee of the National Tuberculosis Association in coöperation with the Hygienic Laboratory of the United States Public Health Service and the Bureau of Animal Industry as the most likely procedure to bring about a better understanding of tuberculin and its action, and enable us to arrive at better methods of use and standardization, and the Commission urges that this work be continued.

DR. HEKTOEN: I second the motion.

SURGEON-GENERAL CUMMING: Any discussion?

The motion was unanimously adopted.

SURGEON-GENERAL CUMMING: I wish to express my appreciation to you gentlemen for having come here and doing all the work you have done. I am sure Dr. Mohler and the National Tuberculosis Association join me in this.

(The meeting adjourned at 4:45 P.M.)

Appendix A

GENEVA

SOCIÉTÉ DES NATIONS LEAGUE OF NATIONS

The Health Committee of the League of Nations has been engaged for several years in the study of the standardization of sera, serological reactions and biological products. The task of carrying out these researches has been entrusted to a group of European and American experts. Results of international importance have already been reached, in so far as the unification of methods to be applied to the titration of several sera and biological products is concerned.

The Health Committee decided at its last session to take up the study of the standardization of tuberculin and appointed a special commission under the chairmanship of Professor Calmette of the Pasteur Institute to examine this problem.

This Commission has come to the conclusion that, before submitting proposals concerning the standardization of methods, it will be necessary to obtain as complete information as possible on the processes of preparation and of titration employed by the various institutes producing tuberculin. For this purpose the Commission has decided to apply to all institutions issuing tuberculin for medical or veterinary use—both official and private—request-

ing them to fill up the questionnaire concerning their methods of preparation and titration of tuberculin.

A copy of the questionnaire is enclosed herewith and we should be grateful if you would kindly complete it and return it to us at your earliest convenience.

Health Section.

Appendix B

LEAGUE OF NATIONS

C. H. 285

HEALTH ORGANIZATION QUESTIONNAIRE REGARDING THE PREPARATION AND TITRATION OF TUBERCULIN

A. Preparation of tuberculin

1. What types of tubercle bacilli do you employ?
2. What is the composition of your medium?
3. What is the initial pH of your medium?
4. For how long is the culture incubated?
5. Is the culture killed before filtration?
   By heat?
   By some other process?
6. Is the volume of the culture reduced by evaporation before or after filtration?
7. Do you carry out filtration by:
   Filter paper No. Mark
   Candle No. Mark
8. Do you sterilize the filtrate thus obtained?
   By heat?
   By some other process?
9. Does the raw tuberculin you prepare represent a mixture of several tuberculins obtained from different types and strains of tubercle bacilli?
10. If such is the case, what are the proportions of human, bovine and avian tuberculins in the mixture?
11. Do you issue your tuberculin in diluted form?
12. If so, to what dilution of the raw tuberculin does it correspond?
13. Do you add to your prepared tuberculin any preservative substance? If so, what is the nature and proportion of the substance added?
14. a. Do you make any preparations other than Koch's raw tuberculin?

    b. If so, please indicate, briefly, the process of their preparation, and their properties and characters.

    c. Are they destined for purposes of diagnosis, or for therapeutic uses?

    d. Do you prepare and issue special dilutions of raw tuberculin or of other tuberculins (which?) for the various cutaneous and intradermal reactions? In what form are these issued?

B. Method of titration of tuberculin

15. Do you make regular titration of your tuberculin?

16. Is titration obligatory by law?

17. Do you make the titration on tuberculous guinea pigs?

18. What is the procedure followed and the type used in rendering the guinea pig tuberculous?

19. Do you make a preliminary test to determine if the guinea pigs are suitable for use in the definitive titrations?

20. By what route do you introduce into the tuberculous guinea pig the tuberculin which is being titrated?

21. Do you carry out titration as against a standard tuberculin, or do you simply determine the toxicity of your tuberculin by its effects on the guinea pig?

22. a. From what laboratory does the standard tuberculin come?

b. For how long have you used it?

c. Do you keep it in liquid or in solid form?

d. Is it stable?

e. From what types has it been prepared?

23. Do you do a preliminary titration before the definite one is carried out?

24. In carrying out the latter do you use one or several methods?

25. Is titration done *in vitro?* If so, is the process based on the principle of

Complement deviation or

Precipitation or

Other biological reaction?

26. Is the titration of tuberculin carried out on the raw product, or after its dilution?

27. Is the tuberculin submitted to any other tests than those for determining its specific toxicity?

C. Additional questions

28. Have you found any difference in the tuberculin produced by different strains of tubercle bacilli?

29. a. If you use a single strain of tubercle bacillus what is its history?

b. What is the character of its growth on different media?

30. What is the relation of surface area of culture medium to volume in each container?

31. What is the resulting weight of tubercle bacilli to 100 cc. of culture medium in the final separation?

32. If you sterilize by heat,

a. What is the temperature used?

b. What is the frequency of exposure to this temperature?

c. What is the total length of time of exposure?

d. What character of heat is used?

33. Has any attempt been made to standardize the guinea pigs used for testing the strength of tuberculin?

34. Has any attempt been made to standardize the tubercle bacillus with which you infect the pigs for testing?

35. How do you determine the dosage?

By counting or

By weight?

36. Is this dose given

Subcutaneously or

Intraperitoneally?

37. If you have any suggestions to offer for the improvement of tuberculin manufacture we shall be glad to have these suggestions enclosed on a separate sheet.

Appendix C

DATA SECURED FROM THIRTEEN FIRMS MANUFACTURING TUBERCULIN

These firms were licensed either by the Bureau of Animal Industry or the Hygienic Laboratory

Number of firms licensed by Bureau of Animal Industry..... 4
Number of firms licensed by Hygienic Laboratory.....11

Total.....15

Thirteen of these firms manufactured and distributed tuberculin as follows:

Production of tuberculin by 13 licensed manufacturing firms and by Bureau of Animal Industry

USE	AMOUNTS IN CUBIC CENTIMETRES			NUMBER OF INDIVIDUAL DOSES		
	1922	1923	1924	1922	1923	1924
Human diagnosis.....	39,471	73,109	101,356	259,242	393,799	506,792
Human treatment.....	170,021	315,945	420,562	680,084	583,700	1,002,170
Pig diagnosis.....	1,691	9,168	11,358	6,764	36,673	45,435
Bovine diagnosis.....	1,010,816	723,368	681,796	4,043,268	2,893,596	5,420,786
Chicken diagnosis.....	502	841	825	2,011	3,367	3,301
Unspecified.....	24,134	34,521	30,508	96,535	138,045	122,056
Total.....	1,246,635	4,156,952	1,246,405	5,087,904	4,049,180	7,100,540
Bureau of Animal Industry production...	2,977,800	2,639,750	3,121,600	8,036,500	12,084,237	15,974,500
Total, United States...	4,224,435	3,796,702	4,368,005	13,124,404	16,133,417	23,075,040

ANSWERS TO LEAGUE OF NATIONS HEALTH COMMITTEE

(*Note:* Where the answers of the following do not appear for corresponding questions it is because no answers were given or they were of no value.)

A. Preparation of tuberculin

Answer 1: Of thirteen firms manufacturing tuberculin

6 use bovine bacilli for bovine tuberculin

5 use human bacilli for human tuberculin

3 use avian bacilli for avian tuberculin

4 use mixed cultures (human and bovine strains are mixed in different proportions for human or bovine tuberculin)

Answer 2: For culture medium

12 use glycerine (5 per cent in most instances, but ranging from 3 per cent to 10 per cent)

5 use veal infusion

5 use beef extract

2 use beef infusion

1 uses Lebig's extract

2 use peptic beef broth

7 use peptone

13 use salts (these vary, usually potassium or sodium phosphate)

Answer 3: The pH of the medium varies from 6.8 to 7.6.

Answer 4: The incubation time varies from 1 week to over 3 months, averaging 8 to 10 weeks.

Answer 5: The cultures are all killed before filtration, by the majority with the Arnold sterilizer with a temperature ranging from 90°C. to 100°C., during one hour; one firm used 1.5 per cent phenol for two days.

Answer 6: The volume is reduced by evaporation

After filtration by 7

Before filtration by 3

Intermittently by 2

(One firm reduces volume of human culture before filtration and the volume of bovine culture after filtration)

Answer 7: The filtration method varies, the majority using paper and candle

Paper and candle, 9

Filter paper alone, 2

Gauze and absorbent cotton pads, 1

Centrifuge and candle, 1

Candle alone, 1

Answer 8: The filtrate is sterilized by

7 with heat

4 with Berkefeld
1 with heat and filtration
1 with phenol
1 does sterility tests after filtration
2 do not sterilize

Answer 9: The raw tuberculin thus prepared comes in 7 cases from unmixed strains and in 6 cases mixed strains, with no two proportions alike. Avian tuberculin, however, is usually from a single avian strain of bacillus.

Answers 11 and 12: Nine (9) firms issue their tuberculin in diluted form and four (4) issue it undiluted. The dilution varies from full concentration to eight one-hundred-thousandths of full strength with no uniformity save in those furnishing undiluted forms.

Answer 13: Nearly all these firms use a preservative, 0.5 per cent phenol being favored in most cases, but 3 out of 13 use none. There is, however, a distinction made between intracutaneous and subcutaneous tuberculin, no preservative being used with intracutaneous and ophthalmic tuberculin. There is no uniform practice.

Answer 14: Eleven (11) firms make other tuberculins than Koch's but use a modified form of Koch's in addition to the following variety of other forms:

1 water extract
5 bouillon filtrate
4 bacillus emulsion
3 tuberculin residue
3 special preparations for the eye (Pirquet and Mantoux)
1 from a specially prepared virulent tubercle-bacillus strain for human therapy.

B. Method of titration of tuberculin

Answers 15, 16, 17: As regards the titration of tuberculin
7 do not test toxicity
6 test by guinea-pig killing potency

There is no uniformity in the method: all are modifications of the Bureau of Animal Industry plan. In two cases State law was obligatory for the test (Michigan and Missouri).

Answers 21 and 22: One firm uses as a standard of tuberculin for comparison a sample from the Bureau of Animal Industry: one uses one from the Hygienic Laboratory, from which none is ever produced. The others use a standard of their own or none at all.

Answer 25: Neither complement deviation nor precipitation is used at all, although one firm uses skin test for human tuberculin and one uses Schroeder's test with Bureau of Animal Industry Standard.

Answer 26: Titration of tuberculin was carried out on the raw product in 2 cases and on the diluted and raw product in 1 case.

Answer 27: The tuberculin was not submitted to any test except, in 7 cases, to a sterility test.

C. Additional questions

Answer 28: Three (3) firms found a difference in the strength of the tuberculin when produced from different strains of tubercle bacilli; two did not find any difference; one found a difference in different crops of the same strain and the others had not investigated.

Answer 29: The history of the strains of tubercle bacilli ranged widely, coming from:

1 from Pennsylvania State Bureau of Animal Industry
1 from Hygienic Laboratory
4 from Bureau of Animal Industry
1 from Nebraska Experiment Station
1 from Saranac Lake
1 from Dr. Ravenel
1 from New York Department of Health
1 from specially cultivated human strain

The growth was carried on Dorset's medium, broth or Glycerine agar.

Answers 30 and 31: The relation of surface area of culture medium to volume in each container varies in each case, ranging from 10 sq. cm. surface area to 100 cc. volume to 150 sq. cm. surface area to 200 cc. volume. In the final separation the resulting weight of tubercle bacilli to 100 cc. of culture medium was not tested by eleven (11). By two firms the resulting weight was 5 gm. per 100 cc.

Answer 32: There is no uniformity in temperature or duration of sterilization. The Arnold sterilizer is used in most cases. The temperature ranges from 90°C. to 100°C. and the time of exposure from one hour, 1 exposure, to 3 hours, that is, 3 exposures on successive days of 1 hour each.

Answers 33, 34 and 35: Six (6) firms have attempted to standardize the guinea pigs used for testing by having the pigs of uniform weight and care.

Nine (9) attempts were made to standardize the dose of tubercle bacilli given to the guinea pigs used in testing the strength of the tuberculin

in 4 cases by counting
in 1 case by weight
in 3 cases by volume
in 1 case by loop

Answer 36: The guinea pigs for this test are infected in six (6) cases subcutaneously, in two (2) cases intraperitoneally.

Answer 37: Only one firm suggests help. It suggests the development of growing tubercle bacilli on synthetic media.

THE INTERPRETATION OF ANNULAR SHADOWS APPEARING IN RADIOGRAMS OF THE LUNGS[1]

E. H. BRUNS AND J. DuB. BARNWELL[2]

The application and perfection of the X-ray examination of the chest during the past twenty years has advanced our study of the clinical course of pulmonary tuberculosis far beyond the possibilities of physical signs and other diagnostic methods. The skill and positiveness of clinicians in the interpretation of physical signs, reaching at times the proportions of conceit, had to be moderated somewhat when roentgenology finally came into its own and the X-ray plate of the lungs could be used as a diagnostic check during life, very much as the autopsy after death. Some clinicians of the old school were reluctant at first to admit the full value of this diagnostic procedure, but as roentgenology developed as a diagnostic measure they began to realize more and more the uncertainty and limitations of physical signs. This was true in the determination of the character and extent of the lesions, but particularly true in the diagnosis of cavities.

Cavities show up in the X-ray negative as dark areas of increased light transmission amid lighter areas of more or less diffuse white cloudiness, or, if the cavity is chronic and possesses a capsule, as an annular shadow. An annular shadow may have no mottling about it. At first it was generally accepted that annular shadows were almost invariably diagnostic of pulmonary cavities. Before roentgenology came into general use it was thought that cavities seldom healed; at least, a cavity the size of a hen's egg or larger never disappeared or only disappeared after many years. This belief was based on the type of cavity easily detected by physical signs or the thick-walled cavity in the upper part of the lung and approximate to the pleura and chest-wall; in other words, cavities surrounded by fibrosis and a thickened and adherent pleura. It is true that such cavities do heal extremely slowly, as a rule, and often never become entirely obliterated. The cavities situated

[1] Published with the permission of the Surgeon-General, U. S. Army, who is not responsible for any opinion expressed or conclusions reached herein.

[2] Medical Corps, U. S. Army, Fitzsimons General Hospital, Denver, Colorado.

more in the midlung, and surrounded by a fairly normal pulmonary parenchyma, are not easily demonstrated by means of physical examination, but are readily seen in the X-ray plate as annular shadows. Such cavities, though large, heal with astonishing rapidity at times. The use of serial roentgenograms in the study of the clinical course of tuberculosis called attention to the fact that annular shadows could disappear within a few months, leaving behind a barely perceptible trace, and, naturally, having accepted the old dictum that cavities, once developed, were there to stay, other explanations for annular shadows were sought. Sampson, Heise, and Brown (1) in 1919 advanced the hypothesis that they could be caused by localized pneumothoraces, and Honeij (2) one year later published a paper on annular pleural shadows. He believes that they could occur as the result of adhesions between the parietal and visceral pleurae, which, under certain conditions, assumed an oval or circular arrangement. In a paper published by Amberson (3) in 1921, and in several papers published subsequently (4) (5) (6), the pneumothorax theory of annular shadows was attacked and the pleurisy hypothesis supported and explained in detail. Amberson viewed the shadows as simple subacute or localized pleurisies, associated at times with umbilication and puckering of the subjacent lung tissue, causing a localized separation of the pleural layers. Barlow and Thompson (7), in their monograph on the diagnosis of small pneumothoraces in pulmonary tuberculosis, stated that a pneumothorax is easily recognized in X-ray plates only when it extends from the anterior to the posterior wall of the thorax, and, as the smaller ones are very seldom situated in exactly that location, their presence cannot be determined by means of the X-ray. Burnham and P. K. Brown (8), in a paper published in 1922, criticized the various interpretations of annular shadows and asserted that

> cavity formation, as met with in lung examinations of tuberculous patients, is recorded in roentgenograms by a sign complex, the essential features of which are more or less well-defined ring-shaped bands of increased density. Within the ring of increased density there is a field of marked diminished density in most cases . . . . Linear markings of lung are not seen. . . . . If a cavity located in a lung field with considerable amount of normal or infected lung in front or back of it is encountered, the sign complex in the roentgenogram of this condition will differ greatly from that of a cavity in which the lung is excavated completely from front to back. The roentgenogram in this instance will record a ring density; but due to lung tissue lying anterior or

posterior to the lung excavation present, the rarefied centre will be absent, and the linear markings of interposed lung will be seen.

According to them, annular shadows are due to cavities.

This is proved by autopsies; by fluid level; by their spherical shape; by the fact that cavities can shrink, change shape and disappear in a short time; and by the fact that artificial pneumothorax produces a lessening of the size of the cavity, or alteration of its shape and a change in location, as serial plates are taken during gradual compression of the lung. In 1924 Casellas (9) published an article, in which he reported four cases showing annular shadows which came to autopsy without any cavities being found to account for the rings. He discussed at length the points of differential diagnosis between cavities and pleural rings, favored the pleural origin of the shadows, and took the extreme view that they should be considered "as of pleural origin in the absence of leading roentgen and physical signs of cavity." Dunham (10) is of the opinion that in the large majority of cases annular shadows are due to cavities.

Thus, we see that a diversity of opinion still exists concerning the interpretation of annular shadows. In pulmonary tuberculosis the presence of a cavity has an important bearing upon prognosis and

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FIG. 1. (CASE 1, T. C.)

Tuberculous lung showing small localized spontaneous pneumothorax at apex. Several small bronchial fistulae present.

FIG. 2. (CASE 2, H. G.)

Localized artificial pneumothorax appearing as an annular shadow in upper and lateral part of lung.

FIG. 3. (CASE 3, MRS. L.)

Pulmonary abscess seen as round shadow at base of right lung. Parenchyma upper lung fields clear.

FIG. 4. (CASE 3, MRS. L.)

Pulmonary abscess seen as annular shadow in upper part of right lung demonstrated at postmortem to be thin-walled abscess with localized artificial pneumothorax over anterior part of lung, the latter not visible in the X-ray film. Negative physical signs.

FIG. 5. (CASE 4, S. T.)

Annular shadows due to cavities in upper parts of both lungs

FIG. 6. (CASE 4, S. T.)

Obliteration of large cavity in upper part of right lung by upper-stage thoracoplasty. Healing of cavity and disappearance of ring in left lung within a few months after thoracoplasty.

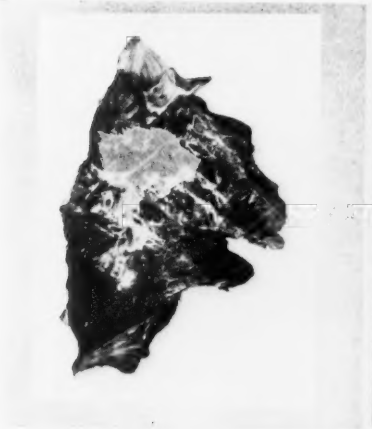

Fig. 1

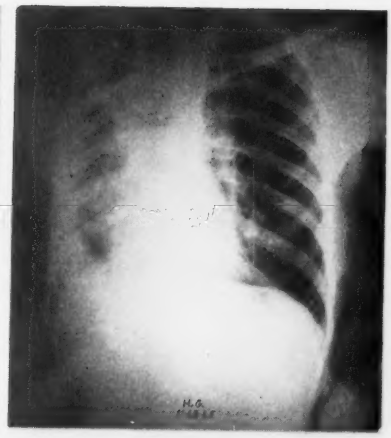

Fig. 2

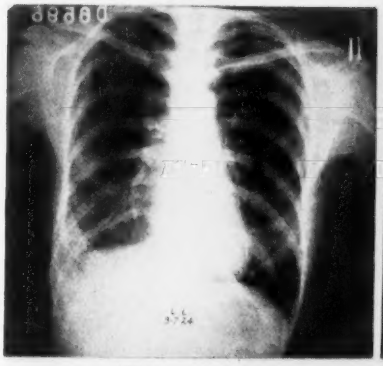

Fig. 3

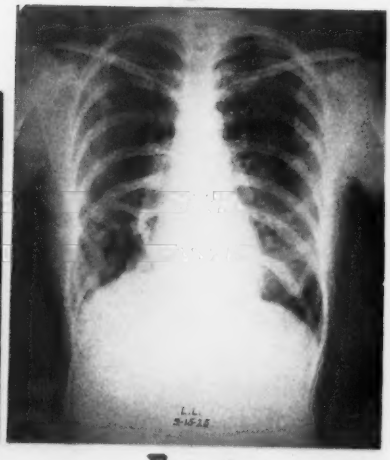

Fig. 4

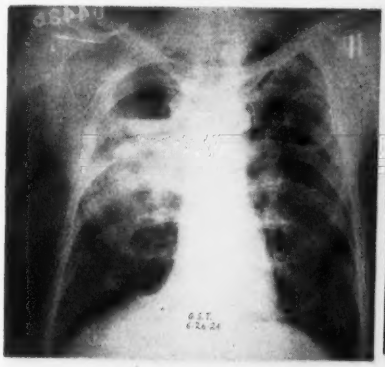

Fig. 5

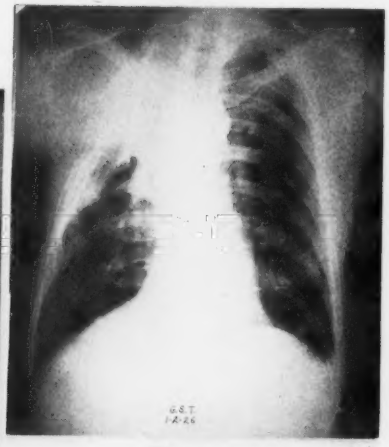

Fig. 6

treatment, and whether or not a ring-shaped shadow seen in the X-ray plate means a cavity or merely a deposit of organized fibrin on the pleura deserves serious and careful consideration. We must admit that not uncommonly cavities fail to produce physical signs. The presence of annular shadows without the physical signs of cavity, or the type of cases in which the existence of cavitation must be diagnosed by the roentgenogram alone, are the ones around which the controversy centres. After studying all the literature on the subject, the cavity origin of the shadow would seem most logical, for, as P. K. Brown has pointed out, there are very conclusive ways, by means of the X-ray, of proving the cavity interpretation and disproving the other views. The pleural and pneumothorax hypothesis are rather fantastical in comparison. Amberson found no difficulty in demolishing the pneumothorax explanation of his Saranac colleagues, but at the same time built up only a theoretical structure in favor of pleural rings. One argument, however, in favor of the pleural origin, which cannot be attacked, is the fact that cases have been reported in which clear fluid could be aspirated by inserting a needle through the chest wall into the ring, and that cases showing rings have come to autopsy in which no cavity could be found in the lungs. We must accept the explanation of those reporting these

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FIG. 7. (CASE 5, R. L.)

Intratracheal lipiodol injection of right lung. Right lung partly compressed by artificial pneumothorax. Large cavity in upper part of lung held out by pleural adhesions. Cavity gave no auscultatory signs and lipiodol failed to enter cavity because communicating bronchus was constricted or plugged.

FIG. 8. (CASE 5, R. L.)

Lipiodol injected through chest-wall and seen in base of cavity. Some escaped through constricted cavity bronchus and can be seen in left primary bronchus.

FIG. 9. (CASE 6, J. J. R.)

Annular shadow at base of right lung. Lipiodol injected direct and seen in bottom of cavity. No definite physical signs of cavity present.

FIG. 10. (CASE 7, J. B.)

Annular shadow at apex. Lipiodol injected direct and can be seen in cavity and bronchial tree.

FIG. 11. (CASE 8, MRS. B.)

Small ring-shaped shadow at hilum of right lung believed to be a tuberculous lymph node with thickened fibrous capsule

FIG. 12. (CASE 9, C. C. D.)

Annular shadows in both lungs, proved by autopsy to be cavities. Cavity in right lung gave no physical signs.

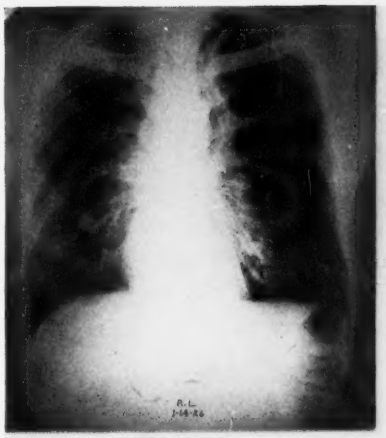

Fig. 7

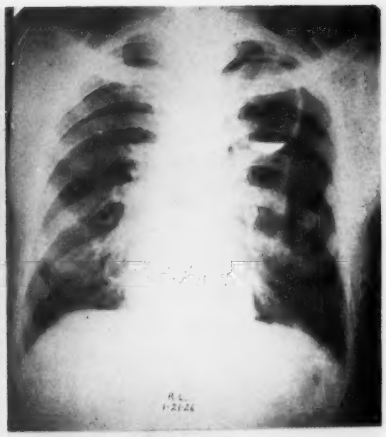

Fig. 8

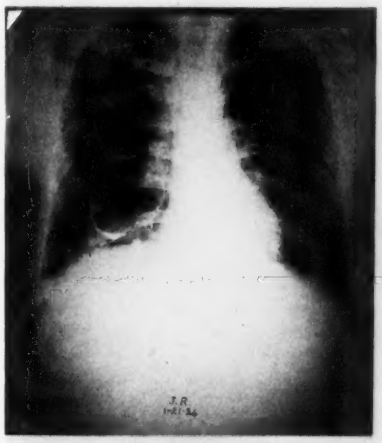

Fig. 9

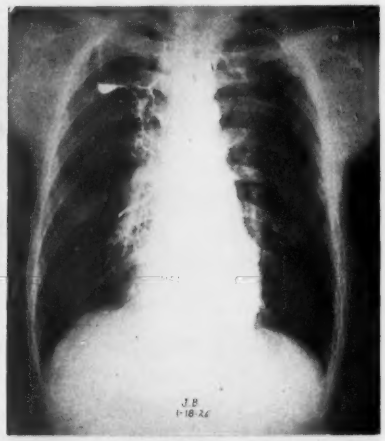

Fig. 10

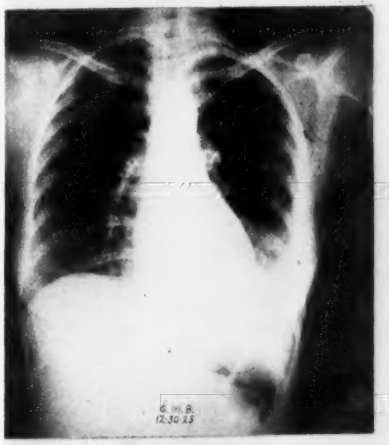

Fig. 11

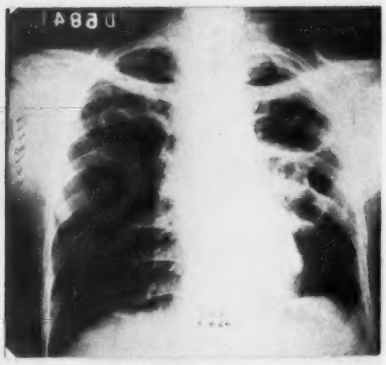

Fig. 12

cases, but at the same time observe that such cases are most exceptional. In one of Amberson's cases, in which a serous fluid was withdrawn from the ring area, a cavity was found at autopsy to account for the annular shadow. During a period of eight years, when one of the writers of this paper witnessed from eighty to one hundred necropsies on tuberculous patients each year, he does not remember seeing a definite X-ray annular shadow which could not be accounted for at the autopsy by the presence of a cavity.

At the Fitzsimons General Hospital, during the past four years, annular shadows have been carefully studied. Cases with annular shadows, in which no cavity signs are present, are reported by the ward officers and are further studied and followed up. Almost invariably the existence of a cavity can be proved. During a period of four years this question has been studied at autopsy, and not a single case showing an annular shadow and diagnosed clinically as a cavity has as yet come to autopsy in which the diagnosis could not be corroborated. In no instance did an annular shadow prove to be pleural in origin. An X-ray view-box, built just above the autopsy table, gives the pathologist an opportunity to check most carefully the X-ray findings. All films which have been made on the case, including postmortem plates, are exhibited, and with these as a guide, the annular shadows can always be identified as cavities, though frequently several sections of the lung have to be made. Three hundred and seventy-five autopsies on tuberculous subjects were studied; 349 had cavities demonstrated at autopsy. In all these cases signs of cavity were seen in the X-ray plates. Although one or both of the writers were present at autopsies, this was again confirmed by reviewing the X-ray reports filed with the patients' clinical records. In addition, we were able to review the plates of 168 of the 349 cases showing cavities at autopsy.[3] Of these, 129 exhibited rings, and in the remainder the cavities were diagnosed only by areas of diminished opacity. In 11, annular shadows were present without any parenchymal mottling surrounding the rings. Only 5 of these gave physical signs of cavity. In 31 cases rings were visible in the X-ray plates, demonstrated at autopsy, but not diagnosed by physical signs (fig. 12). Only rings 3 cm. or more in diameter were considered. We are convinced that a number of the rings would have been classified in

[3] Since 1923 films have been used exclusively at the Fitzsimons General Hospital. Prior to this plates were largely used, and salvaged after having been filed for two years. A number of plates were broken when some shelving toppled over.

the noncavity type by some investigators or by those who favor the teachings of Honeij, Amberson and Casselas. Our pathologist has on several occasions found small localized pneumothoraces over the anterior or posterior part of a lung, not diagnosed before death, and not visible in the X-ray plates. The so called pleural rings could never be found. One autopsy revealed a small localized apical pneumothorax with a bronchial fistula, which was obscured in the roentgenogram by

Fig. 13

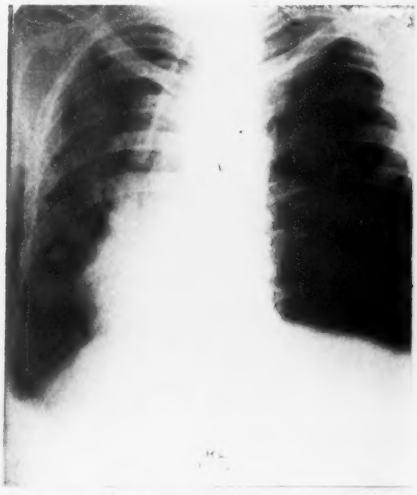

Fig. 14

Fig. 13. (Case 10, H. L.)

Tuberculous left lung with thickened parietal pleura. Lung collapsed by artificial and complicating spontaneous pneumothorax with mixed infection; tuberculous empyema. Opening of mediastinal hernia seen. Hernia caused by extreme left intrapleural pressure.

Fig. 14. (Case 10, H. L.)

Plate showing annular shadow due to mediastinal hernia

a thickened pleura and not diagnosed (fig. 1). Another patient (figs. 3 and 4) was under treatment for ten months for an abscess in the lower part of the right lung. This abscess was first treated with artificial pneumothorax without good results. The lung was then permitted to reëxpand and the abscess finally cured by thoracotomy and cauterization. During a slow convalescence, the patient developed a general neuritis, and a fine ring, 4 x 7 cm., appeared in the X-ray plate, located in the upper part of the right lung. No parenchymal mottling was

present around the ring. No physical signs of cavity could be elicited and no definite symptoms of a pulmonary abscess were present. The nature of this shadow puzzled the roentgenologist and the clinician. An X-ray specialist of national reputation expressed the opinion that it was a pleural shadow. The patient finally died, and the autopsy revealed a localized pneumothorax over the upper lobe of the right lung, not demonstrated in the X-ray plate, but a thin-walled abscess was present to account for the annular shadow. A patient recently came to us in a critical condition. An X-ray plate of his lungs showed a large thick-walled cavity, 8 x 13 cm., in the upper part of the right lung, and another cavity, 5 x 5 cm., in the midportion of the left lung. Below the cavity in the right and surrounding the cavity in the left lung was a rather diffuse parenchymal mottling. This patient stated that he had been told that his left lung was in fairly good condition and that the annular shadow was a pleural ring. This shadow was diagnosed a cavity, after careful X-ray study. The ring contained a fluid level, which varied from time to time and was spherical in shape. The physical signs were fairly definite of cavity. Following a thoracoplastic operation on the right side, the cavity in the left lung healed completely within a few months (figs. 5 and 6). This case shows the danger of diagnosing such shadows as of pleural origin, for the patient had a feeling of false security, believing that his left lung was only slightly involved, until he drifted into a critical condition and only a miracle saved him.

Although postmortem evidence would indicate that the vast majority of rings visible in the roentgenograms of tuberculous patients are due to cavities, other unusual causes for these rings undoubtedly exist. Among such causes may be included abscess, tumor, cyst, pleural deposits, localized pneumothoraces, interlobar pneumothoraces, tuberculous bronchial lymph nodes, emphysematous blebs, hernia of the mediastinum, etc.

When physical signs of cavity are absent, steps should be taken to eliminate the other sources of annular shadows, and no effort should be spared in deciding the question. As already mentioned, the correct interpretation of annular shadows has a very important bearing on prognosis and treatment. The absence of involvement around the ring is no proof of the nonexistence of a cavity. A well-localized lesion frequently caseates, liquefies, and is eliminated in its entirety, leaving behind a ring in an otherwise normal-appearing lung field. The presence of a fluid level is very strong evidence in favor of a cavity, and al-

most conclusive if the fluid level varies, or disappears after the patient is made to cough out or drain his lungs. Plates taken with the patient in an oblique position, and showing a ring with almost as much depth as width, is good proof of the existence of a cavity. Changes of size and position, as the lung is gradually compressed in artificial-pneumothorax treatment, is a certain manifestation of the presence of a cavity. Recently we have used intratracheal injections of lipiodol. In some cases showing apical rings we have injected lipiodol through the chest-wall directly into the cavity. If the fluoroscopic examination or X-ray plate, after the intratracheal injection, shows the oil within the annular shadow, it substantiates the diagnosis of cavity (figs. 7 and 8). When the oil is injected directly into the cavity, fluoroscopic examination reveals the globular shape of the shadow as the lipiodol settles in the base of the cavity, giving a fluid level as it would appear in the bottom of a sphere (fig. 9). The presence of this opaque medium in the bronchial tree proves the existence of a bronchial communication with the annular shadow, which is rather conclusive evidence of a cavity (fig. 10). Localized pneumothoraces, when situated laterally, can produce annular shadows (fig. 2). Such shadows are usually flattened rings, situated laterally or at the top of the lung, and contain no lung markings. Localized pneumothoraces, artificial or spontaneous, producing shadows of this description, are not uncommon. If spontaneous they can easily be confused with cavities, and a differential diagnosis may be rather difficult. They may even communicate with a bronchus, which confuses the etiology still more. In favor of pneumothorax is absence of the typical physical signs and symptoms of cavity, and the rapid disappearance of the ring. Rings at the hilum may be due to a tuberculous lymph node, as we were able to demonstrate at one autopsy, and diagnosed in the case of another patient who recovered. A middle-aged woman suddenly developed an aspiration tuberculous bronchopneumonia at the base of the right lung. This was probably due to the breaking down and rupture into a bronchus of a caseous tracheobronchial lymph node (fig. 11). A ring could be seen at the supposed site of this lymph node. No evidence of tuberculous involvement existed in any other part of the right lung or in the left lung. The tuberculous bronchopneumonia resolved and completely disappeared under selective artificial pneumothorax, but the ring still remains. In a recent case which had been receiving artificial pneumothorax on the left side for some time, a spontaneous pneumothorax occurred and the intra-

thoracic pressure became quite high. A film made at this time shows marked mediastinal displacement toward the right with a large annular shadow evident in the midpart of the right lung field, and partly overlying the displaced heart shadow. The appearance of this shadow was quite suggestive of a cavity, but was not diagnosed as such. The patient died, and the autopsy revealed a large hernia of the mediastinum into the right side of the thorax (figs. 13 and 14).

CONCLUSIONS

1. Annular shadows visible in the X-ray chest plates of phthisical patients are due to cavities in the vast majority of cases.

2. Postmortem studies made at the Fitzsimons General Hospital are overwhelmingly in favor of the cavity explanation of annular shadows.

3. The existence or nonexistence of a cavity in pulmonary tuberculosis is so important from a prognostic and treatment point of view that, in doubtful cases, every effort should be made to make a positive diagnosis by excluding other causes of annular shadows.

4. If an annular shadow is present in the roentgenogram of a tuberculous lung, it should be considered as being due to a cavity until proved otherwise.

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WHAT CAN BE ACCOMPLISHED BY SURGERY IN ADVANCED PULMONARY TUBERCULOSIS[1,2]

WILLIAM H. THEARLE[3]

Operative procedures for pulmonary tuberculosis are still new and as yet not appreciated by most medical practitioners and even general surgeons, while among the public at large surgery in this disease is either unheard-of treatment or associated with unmerited misconceptions.

The great advances in this field of thoracic surgery on the Continent of Europe during the past ten years, and the high annual mortality from consumption in this country, in spite of modern hygienic measures and sanatorium treatment, have at last awakened phthisiologists to the importance of surgery in treatment. The need for such operative help has recently been forcibly brought to our attention by Alexander (1), who estimates that nearly 3 per cent, or 30,000, of all persons with phthisis in the United States, are proper subjects for surgical therapy.

The increasing resort to thoracoplasty throughout the country attests its present growing popularity. The professional education and public enlightenment that will result therefrom in the next decade should materially lower the present mortality, as well as improve the results of thoracoplasty, by earlier operation at a more favorable stage of the disease.

The surgical measures in their relative order of merit in pulmonary tuberculosis are extrapleural thoracoplasty, radical phrenicotomy, extrapleural pneumolysis and cavity drainage.

Cavity Drainage by cautery is of rather limited value, but will occasionally be indicated as an improving measure for the toxemia of solitary tuberculous cavities with mixed infection, which thoracoplasty has failed to collapse fully.

Extrapleural Pneumolysis, usually performed to collapse apical cavities

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[2] Read before the Medical Society of the City and County of Denver, Colorado, February 16, 1926.

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(apicolysis), is theoretically an ideal procedure, but none of the various filling schemes so far advocated have proved entirely satisfactory, as they fail to obliterate such cavities permanently. Our experience with 12 pneumolyses (one pectoral muscle and eleven gauze-tampon fillings), performed over a year ago, is that partial cavity expansion occurs through scar contraction, as the large extrapleural space created by operation fills with granulation tissue. This procedure is considered to be indicated only in exceptional cases after thoracoplasty for the collapse of small remaining apical cavities.

Phrenicotomy: Paralysis of half the diaphragm by radical extraction of the cervical and upper mediastinal portions of the phrenic nerve is a relative innovation in phthisiotherapy during the last five years, that is deserving of more extensive use. Authorities of the Continent state that phrenicotomy alone is not a curative measure in advanced pulmonary tuberculosis, but Alexander (1) believes that it will cure some cases of early unilateral tuberculosis which are not making progress under sanatorium regimen alone. In an experience of 82 phrenicotomies, we have found the operation valuable in unilateral phthisis with predominantly basal lesions, in artificial pneumothorax when basal adhesions prevent full compression, and preliminary to complete extrapleural thoracoplasty. Sauerbruch (2) considers phrenicotomy also of value to test the status of suspicious lesions in the better lung before thoracoplasty.

Extrapleural Paravertebral Thoracoplasty, a resection of various lengths of the first eleven ribs in two or three stages, is the most radical and commonly performed operation for pulmonary tuberculosis. Its object is (1) collapse of one lung to a degree proportional to the extent of involvement, and (2) surgical rigidity of half the chest.

Lilienthal (3) states that fixation of the hemithorax is really the operative desideratum in thoracoplasty and is quite as vital as the pulmonary collapse, because it rests the diseased lung by reducing to a minimum the respiratory movements. Thoracic rigidity is undoubtedly a most important factor in pulmonary healing after thoracoplasty, but it is believed that adequate surgical collapse of cavities is the prime necessity in ulcerative phthisis, especially with cavitation of any size.

Lilienthal also believes that, in this operation, one can commit the error of removing too long sections of ribs, so that regeneration of bone is either greatly delayed or may never occur, and much of the rest accomplished by rigidity be thus lost. This is a valuable warning, although we do not believe that any hard and fast rule can be formulated

for the length of paravertebral costectomies, because this must be determined by a thorough study of the requirements present in each individual case.

The local indication for surgical collapse is chronic advancing phthisis with predominantly unilateral involvement, when pleural adhesions prevent pneumothorax therapy. The contraindications are those applicable to any similar major surgical procedure. Archibald (4) has stated that tuberculosis advanced enough to need thoracoplasty is practically never one-sided; contralateral activity at the base or hilum of the better lung is an absolute contraindication to operation, but we do not maintain such an exacting attitude toward upper-lobe lesions unless advanced. The reason for this view is that in such patients one lung is usually irretrievably diseased and often functionless, while the other continues competent to perform the respiratory function, and the cessation of toxemia by successful thoracoplasty in selected cases of this type will not infrequently result in arrest of the opposite apical lesions.

The special preoperative measures of value are radical phrenicotomy (before a complete or eleven-rib thoracoplasty), full doses of digitalis for the myocarditis which is invariably present in advanced tuberculosis of any duration, and emptying of secretions from pulmonary cavities before operation.

Accidental invasion of the pleura, and the danger of injury to the subclavian artery or brachial plexus in resection of the deeply located first rib, constitute the unusual features of this operation, which we have performed under nitrous-oxide anesthesia for over eighteen months without any unfavorable effect on the lungs.

Increasing experience with thoracoplasty has strengthened our earlier conviction that this operation should always be performed from below upward as advised by Sauerbruch.

Complications peculiar to thoracoplasty are (1) early cardiac failure due to myocarditis, together with the changed thoracic relations incident to this operation, which is combated by full and continued digitalis therapy and proper support of the operated half of the chest without early pulmonary compression; (2) aspiration pneumonia, the most feared of all complications, which is minimized by preoperative emptying of cavities, frequent changes of posture (5) and *no* morphine or opiates (except in pyopneumothorax cases), which in pain-relieving doses abolish cough for twenty-four to forty-eight hours with retention of sputum, and resulting high temperature and added toxemia. There is thus more post-

operative pain, especially during the first days, which is rendered bearable by other analgesics that do not inhibit the desired early coughing and emptying; (3) tuberculous extensions and activation; and (4) pneumonia.

Bull (6) reports a late mortality of 39 per cent in 82 cases, mostly from tuberculosis in the unoperated lung, while Archibald (4) recently stated that this probably occurs in 30 per cent after thoracoplasty. This is believed to be chiefly due to continued toxemia from incompletely collapsed cavities after operation, which emphasizes (1) the importance of earlier surgical collapse in tuberculosis, (2) the realization by the patient that thoracoplasty is but a mechanical procedure that provides conditions under which fibrosis and healing are facilitated, and (3) the necessity for supplementary surgical procedures to cure remaining lesions when Nature fails to accomplish this in a reasonable time. Intratracheal injections of lipiodol are often invaluable in the localization and determination of incompletely collapsed cavities.

RESULTS

Our experience with extrapleural thoracoplasty comprises 85 tuberculous patients, many of whom were far-advanced cases and poor surgical risks that did not fulfill the accepted operative indications. Our results of 30 per cent of all cases arrested and 38 per cent improved are very gratifying, even with a 15 per cent mortality for the series; (that is, early cases 4 per cent, far-advanced and spontaneous pyopneumothorax 21 per cent, and 9 per cent due to operation). This mortality rate is relatively high, but is to be expected with the desperate risk so often associated with thoracoplasty in far-advanced pulmonary tuberculosis.

FIG. 1. CASE 1 BEFORE OPERATION

FIG. 2. CASE 1 FOUR MONTHS AFTER PHRENICOTOMY

Cavity reduced 75 per cent

FIG. 3. CASE 2 BEFORE OPERATION

FIG. 4. CASE 2 FIVE MONTHS AFTER PHRENICOTOMY

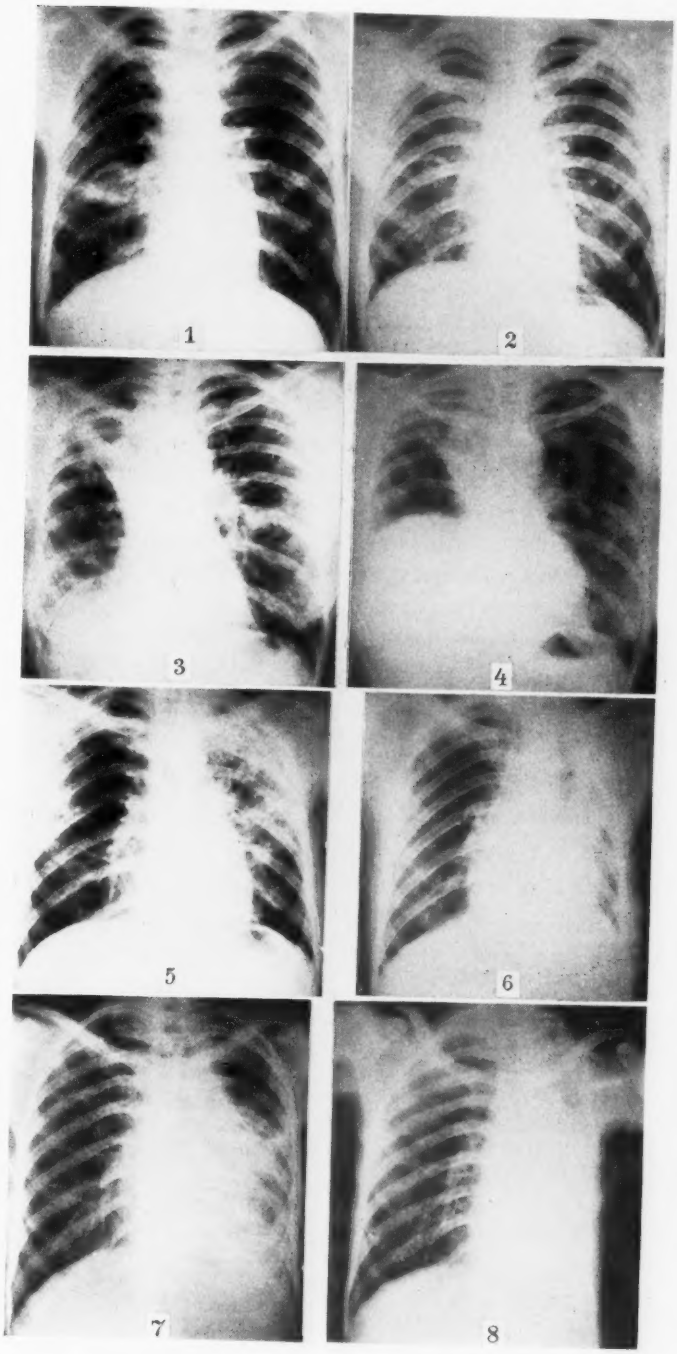
High rise of right diaphragm. Lesions now more fibrous and discrete

FIG. 5. CASE 5 BEFORE THORACOPLASTY

FIG. 6. CASE 5 THREE MONTHS AFTER OPERATION

FIG. 7. CASE 6 BEFORE THORACOPLASTY

FIG. 8. CASE 6 TWO MONTHS AFTER THREE-STAGE OPERATION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Case Reports

Case 1: Male, age 29, with active tuberculous lesions in all lobes of both lungs, and 3 cm. cavity in right lower lobe; right diaphragmatic adhesions; 16 cm. of right phrenic nerve extracted August 28, 1925; X-ray six months later showed cavity reduced 75 per cent and lesions fibrous and discrete. Cough diminished and sputum reduced from ¾ cup to 15 cc. daily. Condition improved. (Figs. 1 and 2.)

Case 2: Female, age 38, with active tuberculous lesions in all lobes of both lungs and 3.5-cm. cavity right upper lobe. Also has anal fistula. Frequent cough, with one cup of sputum daily. On August 31, 1925, right phrenicotomy (15 cm. extraction). X-ray five months later showed high rise (10 cm.) of right diaphragm, and lesions smaller and more fibrous in right lung. Sputum now ¼ cup daily, cough moderate, 13 pounds gain in weight. Improvement so far has been marked. (Figs. 3 and 4.)

Case 3: Male, age 49. Tuberculosis of ten years' duration, with active lesions in all lobes of both lungs, with large cavities in upper lobe of each lung, on the right side involving nearly the whole lobe, and tuberculous broncho-

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FIG. 9. CASE 3 BEFORE OPERATION

Large cavities of upper lobe of each lung with tuberculous bronchopneumonia of right lung below cavity. Left cavity traced for definition.

FIG. 10. CASE 3 FIVE MONTHS AFTER RIGHT PNEUMOLYSIS

Right cavity reduced 50 per cent, with inactive fibrous lesions of right lower lung. Cavity of left lung 70 per cent smaller.

FIG. 11. CASE 3 SIX MONTHS AFTER RIGHT THORACOPLASTY (UPPER STAGE ONLY, 7 RIBS)

Cavity in left lung disappeared. Very small remaining cavity of right upper lobe which required cavity drainage through pneumolysis scar. Note fibrosis and clearing up of both lungs with relief of toxemia.

FIG. 12. CASE 4 BEFORE ARTIFICIAL PNEUMOTHORAX

FIG. 13. CASE 4; ACUTE RIGHT PYOPNEUMOTHORAX (SPONTANEOUS) WITH COMPLETE COLLAPSE OF RIGHT LUNG

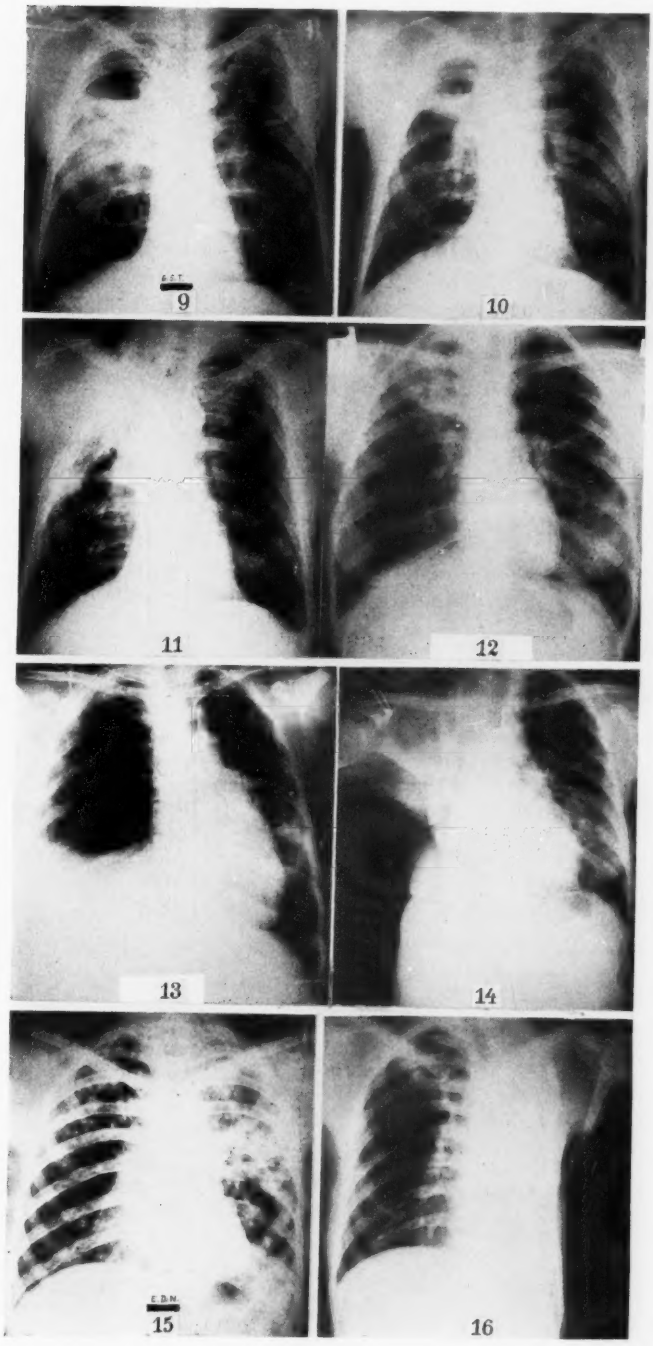
FIG. 14. CASE 4; COMPLETE COLLAPSE OF RIGHT LUNG AND OBLITERATION OF LEFT PLEURAL CAVITY BY MULTIPLE THORACOPLASTIC OPERATION

Tuberculosis arrested

FIG. 15. CASE 7; FAR-ADVANCED LESIONS THROUGHOUT LEFT LUNG AND ADVANCED LESIONS IN RIGHT UPPER LOBE

FIG. 16. CASE 7 SIX MONTHS AFTER THORACOPLASTY

Left lung well collapsed. Lesions in right upper lobe inactive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pneumonia in right lung below cavity. Also tuberculous laryngitis. Patient quite pale and septic. with high temperature and night-sweats. Cough frequent and distressing, with dyspnea and 2 cups sputum daily, frequently quite foul. Marked gastrointestinal symptoms. An apparently hopelessly ill man who appeared to be approaching a terminal state; and, although a very poor and desperate operative risk, in view of his surprisingly good heart action and pulse a right extrapleural pneumolysis was performed through anterior resection of 2nd rib, November 5, 1924. Entire right upper lobe collapsed and maintained by gauze tampons. Stormy convalescence for next week, but the rapid and progressive improvement in patient's condition has seemed magical. Voice returned in three weeks, fever disappeared with return of appetite, gain in weight and reduction in sputum and cough. Large extrapleural space slowly healed with granulation tissue in six months, sputum reduced to $\frac{1}{3}$ cup per day. X-ray showed marked improvement in both lungs with reduction in cavities. Cavity in right lung reëxpanded somewhat by scar contraction, as pneumolysis wound healed with increase in sputum and cough, and some return of daily elevation of temperature.

On June 22, 1925, right upper-stage extrapleural thoracoplasty performed (resection upper 7 ribs). This was soon followed by improvement, but the thick scar from pneumolysis prevented complete collapse of the cavity, and the highly toxic contents (mixed infection) of even this small remaining cavity caused return of toxemia in five weeks. On July 28, 1925, this cavity was drained by cautery through the pneumolysis scar. The patient has since continued to improve; sputum negative for tubercle bacilli since last fall (first time in ten years). Patient seldom coughs now; sputum scant and mucoid; he is ambulatory and walks five miles each day without fatigue; appetite excellent, with gain of 40 pounds in weight. At present there is scant drainage from the cavity, which we hope to obliterate shortly and heal by a plastic operation. The unexpected remarkable result in this far-advanced case illustrates the great possibilities of thoracoplastic surgery in tuberculosis. (Figs. 9, 10, 11, 19 and 20.)

Case 4: Female, age 30. Tuberculosis for three years, with active lesions in right upper lobe and multiple cavitation, inactive in left upper lobe. Cardiac arrhythmia with extrasystoles. Moderate cough with $\frac{1}{2}$ cup sputum daily. Progressive improvement under artificial pneumothorax till March 28,

FIG. 17. CASE 4 AT PRESENT

Note small obvious deformity even with complete collapse of right chest when dressed. Some scoliosis present.

FIG. 18. CASE 6 BEFORE THORACOPLASTY (DRESSING ON NECK IS FOR PHRENICOTOMY)

FIGS. 19 AND 20. CASES 3, 5, 6, 7 (FROM LEFT TO RIGHT) AT PRESENT

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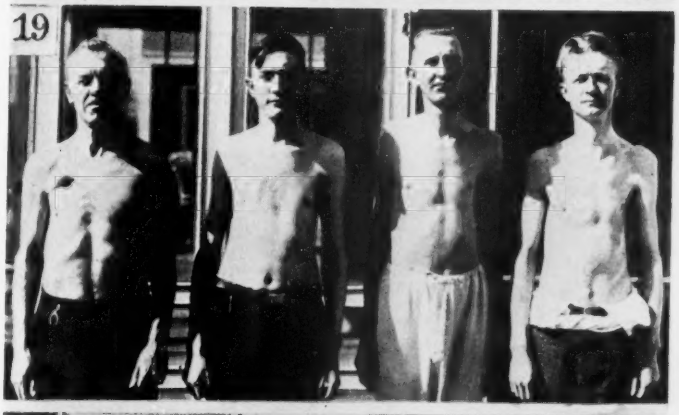
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1924, when spontaneous pneumothrax occurred and acute pyopneumothorax promptly developed. The patient became acutely ill and very toxic, with high temperature and weak irregular pulse.

On April 2, 1924, a single-stage right extrapleural thoracoplasty (2nd to 11th ribs, since condition did not warrant resection of 1st rib) performed under paravertebral anesthesia. Pus aspirated from pleural cavity. Operative convalescence very stormy; wound soon became infected from pleura and aspirations; thoracotomy became necessary for drainage and pleural irrigation. Weight dropped to 80 pounds.

The patient improved quite slowly; had febrile exacerbations for several months; liver and spleen became enlarged; urine contained albumen frequently and at times casts. Blood sugar rose to 220 with glycosuria. Amyloidosis suspected. However, with tonic treatment, heliotherapy, blood transfusions and selected diet, some lasting improvement was finally obtained; and the patient has since required four minor operations for removal of sinuses and infected rib-ends, resection of axillary segments of the 3rd to 8th ribs with unroofing of the remaining pyothorax cavity, and a parasternal resection of 2nd, 3rd and 4th ribs, to completely obliterate her right pleural cavity. X-ray shows marked collapse of right chest with scoliosis; deformity is invariable in such cases, but is not so noticeable when the patient is dressed. At present she is ambulatory with a small sinus in the region of the 10th rib; liver and spleen not enlarged; blood sugar 100 to 115 (diet still restricted in carbohydrates); urine negative; weight 115 pounds; occasional cough with scanty sputum, negative for tuberculosis. Improvement marked; tuberculosis apparently arrested. (Figs. 12, 13, 14 and 17.)

Case 5: Male, age 24. Tuberculosis diagnosed January, 1925. Pulmonary lesions active in both lobes of left lung with small upper cavitations, and inactive in right lung. Sputum, $\frac{3}{4}$ cup daily. On October 26, 1925, left phrenicotomy, and November 4 and 13, 1925, two-stage left paravertebral thoracoplasty performed. X-ray shows left chest adequately collapsed; has slight morning cough, with little mucoid expectoration. Twelve pounds gain in weight, and progressively improving, and should continue to eventual clinical cure. (Figs. 5, 6, 19 and 20.)

Case 6: Male, age 26. Three years tuberculosis, with active lesions in both lobes of left lung and multiple cavitation, upper lobe replaced by large cavity; scattered activity in right lung, with 2-cm. cavity in right apex. Considerable cough, with 2 to 3 cups of sputum per day; marked dyspnea; weight 98 pounds. Discharged from Navy for myocarditis. A far-advanced case with bad heart and functionless left lung. Very poor and doubtful surgical risk; three-stage thoracoplasty performed (September 23 and October 5 and

21, 1925), preceded by left phrenicotomy on September 16, 1925. X-ray shows excellent collapse of left lung; present weight 123 pounds and still gaining; slight cough with scant mucoid sputum; ambulatory with no dyspnea and markedly improved even at this early data. (Figs. 7, 8, 18, 19 and 20.)

Case 7: Male, age 28. Five years tuberculosis with active lesions in both lungs; left lobes replaced by multiple cavities; advanced lesions in upper right lobe with multiple very small cavities. Dyspnea, with considerable cough and 2 cups of sputum daily; toxic myocarditis; weight 91 pounds. A far-advanced case, with bad heart and functionless left lung, really too advanced for thoracoplasty. However, two-stage left thoracoplasty performed March 4 and 27, 1925. Patient desperately ill after second stage because of myocarditis. Weight dropped to 81 pounds. Patient now living at home; weight 118 pounds; no dyspnea; occasional cough, with scant mucoid sputum, negative for tubercle bacilli; X-ray shows left lung completely collapsed. This is the most advanced thoracoplasty we have performed, and the patient's remarkable progress makes us hopeful that it will continue to a clinical cure. (Figs. 15, 16, 19 and 20.)

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DEFLATION OF THE PLEURAL CAVITY IN THE TREATMENT OF SPONTANEOUS PNEUMOTHORAX[1]

WALTER H. WATTERSON[2]

ETIOLOGY

Spontaneous pneumothorax in the sense that it is produced apart from external influences, does not usually occur. Perforation of the pleural cavity, either from within or without, immediately disturbs the intrapleural suction by producing a pneumothorax. We here consider perforation from within.

The breaking down of a subpleural tubercle of the lung through the visceral pleura, is the most common cause (Bushnell (1)). Other causes mentioned are tearing of an old adhesion from straining or violent coughing (1), rupture of superficial cavities which are not walled off from the pleural cavity (Alexander (2)), and bursting of an emphysematous bleb (Barlow and Kramer (3)) by a cough, or otherwise (2). Empyema discharging through a bronchus, and rupture of a mediastinal growth, as in the case B. J. K., reg. no. 13,261, of erosion of carcinoma of the esophagus through the mediastinal pleura, as shown by autopsy at this hospital October 21, 1925, are mentioned as further causes of spontaneous pneumothorax; but, since these are secondary to some other pathological changes, the primary condition should be the attributive factor, as pneumonia, abscess of the lung, or carcinoma.

CLASSIFICATION

We have several classes of spontaneous pneumothoraces, depending on the course of the disease and the resulting pleural adhesions. In the rapid type of pulmonary tuberculosis, when few pleural adhesions occur, we usually have a generalized pneumothorax and it is to this condition that I refer in this paper.

When pleural adhesions limit the spread of air in the general pleural cavity, we have a partial pneumothorax, or an encysted pneumothorax

[1] Published by permission of the Medical Director, United States Veterans Bureau.

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when the lung does not collapse as a whole. Case 2, reported herewith, was an example of all three types of spontaneous pneumothorax, as shown by the accompanying X-rays; at first, partial in the upper right side, later encapsulated in the lower right side, and then generalized in the left side.

In the latter two types, the distress to the patient is relatively mild, or even not perceptible by him. The physician often discovers the unexpected condition, either by the X-ray or physical examination. No present infallible proof of the presence of a small pneumothorax exists, except actual separation of pleural surfaces (1). This has also been noted by Gray (4) and Dunham (5).

APPARATUS AND TECHNIQUE

For the treatment of generalized pneumothorax by deflation, the Robinson artificial-pneumothorax apparatus is reversed, the proximal bottle being filled with water, while the distal bottle is dropped to a lower level and the water siphons from the proximal into the distal bottle, creating a vacuum in the proximal bottle. Manometric readings are made before deflation and after removal of each 200 cc. of air, as measured by the water displacement in the proximal bottle. The technique, otherwise, is the same as that for giving a pneumothorax as described by Barlow and Kramer (3) and the technique and apparatus as described by my article in 1914 (6).

The extreme emergency of the condition prevented manometric readings before deflation in case 2, a bilateral pneumothorax. As noted in the records, the normal negative intrapleural pressure or suction of 5 mm. of mercury on expiration to 10 mm. of Hg on inspiration (MacLeod (7)), is changed to a more or less positive pressure, our greatest positive pressure being that of case 4, +6 to +9, with many adhesions, as compared with case 3, +2.5 to +3, without many adhesions.

Our readings were all made with a water manometer, and will be so recorded. For those wishing to compare these readings with the mercury manometer, it is recalled that 1 cm. of mercury pressure is equivalent to 13.6 cm. of water pressure.

CONTENTION

Case 1, as noted by the clinical history, suffered a spontaneous pneumothorax while the lung was collapsed therapeutically. However, we

do not think that artificial pneumothorax caused the spontaneous pneumothorax. It is asserted that spontaneous pneumothorax has, however, greatly increased since artificial pneumothorax has been extensively practised (2). Bronfin reports 6 cases (8); Krause and Heise report one rupturing just at the point of insertion of a pleural adhesion. Matson, Matson and Bisaillon report 16 cases (8), while later Bronfin gathers reports on 51 cases from various authors (8).

The accident has occurred but once, in case 1, in patients operated upon here. This covers over 200 paracenteses in some 30 cases. A report on the intrapleural pressure, as studied in these cases, is in progress, and will be prepared during the year. This, with careful X-ray confirmation and fifteen years' experience in giving therapeutic pneumothorax, causes me to doubt the increase of spontaneous pneumothorax since the advent of artificial-pneumothorax treatment. The fact that in the study of these cases a long period often elapsed between the last inflation and the spontaneous pneumothorax, and that there is a greater frequency of spontaneous pneumothorax now recognized by the aid of the X-ray, convinces me that in not a few, as with case 1, the spontaneous pneumothorax was coincident with and not a result of artificial pneumothorax.

In case 1, the patient's chest was very large, and the added air in the pleural space following the rupture was not more than a third of the air already present. Deflation of 700 cc. of air gave complete relief from symptoms though not a complete return of viscera to their position before the accident.

DISCUSSION OF CASES

Case 3 was an example of that spectacular relief by deflation that approaches the miraculous in the eyes of the patient and friends. This case came as near being spontaneous as one can imagine. Up to this time pulmonary tuberculosis had never been diagnosed. The patient was in the hospital pending nephrolithotomy, and three days after this operation developed an increasing cough and pain in the left chest, which on physical examination was diagnosed as spontaneous pneumothorax. The symptoms became worse, X-ray confirmed the diagnosis and when deflation was begun the patient was *in extremis*. The manometric reading was +2.5 to +3. Readings were taken after each 200 cc. of air removed. The cyanosis, extreme dyspnea, rapid breathing, feeble

pulse, and cold sweating abated until 1800 cc. of air was removed, when the reading was −4.5 to −1, and the patient was quite normal in appearance and behavior. This deflation was done slowly, covering a period of about thirty minutes. X-ray following the deflation showed about a half-expansion of the lung and a month later complete expansion. The patient left the hospital, and a recent report states that he is in California and in fairly good health.

Cases 4, 5, 6, 7 and 8 all developed pneumothorax near the end of a short struggle with the pneumonic type of pulmonary tuberculosis. Deflation was done to relieve the distress of the emergency. Their case records tell the story.

We were successful in relieving all but one of these, case 8. Case 2 had almost no functionating lung on the right side, a large cavity occupied the space usually taken by the middle lobe, and the heart was drawn well into this space. This displacement of the heart into a large cavity has been noted frequently by us and by Bushnell (9) and by Gray (4), and is of diagnostic value.

As previously stated, this patient also had a partial and an encysted pneumothorax on the right, the partial pneumothorax causing the characteristic deviation of the trachea, as described by Barlow and Thompson (10). He then suddenly developed spontaneous pneumothorax on the left side. Following deflation, relief was immediate. Only 750 cc. of air was removed, but this gave sufficient functionating lung in this, the only remaining lung possible to restore, and the X-ray showed an almost complete expansion next day, and a definite cavity in the apex,—the source of the pneumothorax on this side. The manometer on the following day showed a negative intrapleural pressure, and the needle was removed without further deflation, since the patient was very comfortable and remained so for over a year, when other tuberculous complications resulted in his death.

Report of Cases

Case 1: A. N. M., reg. no. 8,028, admitted February 19, 1924, for treatment of pulmonary hemorrhage, which had persisted for a week and was the first subjective symptom of his present illness. He had lost about 20 pounds in weight, now weighing 155.5 pounds stripped and was 73.5 inches tall. Military, post-war, family and personal histories were negative up to a week ago; occupation, metal finisher at Detroit, but had lived in Tennessee before the war.

Our examinations showed that the lung above the 2nd rib, right, was doubtless the source of the hemorrhage. The chest stereo showed definite infiltration of the right upper lobe with a small cavity in the apex, which had ruptured into the right pleural cavity, causing a partial pneumothorax of the superficial type. *Laboratory reports:* Sputum positive Gaffky 4, Wassermann negative, urine normal. Our diagnosis was tuberculosis, pulmonary, far advanced C.

The profuse pulmonary hemorrhage would not respond to ordinary treatment; so artificial pneumothorax was begun February 22, 1924. The manometric readings were −7 to −2 before inflation and after administering air the negative pressure gradually lessened until it was −5 to −3 after 1000 cc. of air was given. Three days later 1400 cc. of air was given, the hemorrhage not being stopped by the first inflation, but checked after this later inflation. The manometric reading was now −1 to 0. Following this, 19 inflations were given up to January 16, 1925, when the lung showed almost complete collapse, as shown by X-ray.

At this time, physical examination, with X-ray and clinical study showed some activity in the opposite lung. No further inflation was given. On the night of April 8, 1925, the patient experienced a pain in the mediastinum which was followed by dyspnea, higher pulse-rate and a temperature rise to 102.9°F. This did not subside, and an X-ray was requested, which showed a definite spontaneous pneumothorax superimposed on the artificial pneumothorax of the right side.

Deflation was done. The manometric reading was +1.5 to +3; we removed 700 cc. of air from the right pleural space. The cyanosis and mediastinal pain subsided at once, and the manometric reading was −3 to −1. The pulse and temperature soon became quite normal.

Two months later, on his own request, the patient was discharged against medical advice, and has since continued treatment in the Southwest, and at the same time has done some work.

Case 2: E. A. L., reg. no. 3,903, admitted October 3, 1922, for treatment of tuberculosis, pulmonary, far advanced C, and pleurisy, chronic, at both bases, with tuberculous enteritis. Later tuberculous laryngitis complicated the case. The entire right lung was markedly involved with cavitation, partial pneumothorax and fibrosis throughout, the middle lobe being replaced by the heart deviated to the right of the left border of the sternum. An X-ray of March 29, 1923, showed definite encysted pneumothorax at the right base and increased partial pneumothorax over the upper.

On the morning of March 26, 1924, the patient had a left spontaneous pneumothorax and, when the lung was in collapse, air hunger and cyanosis were marked. Knowing the condition of the opposite lung and seeing the critical

condition of the patient, we removed 150 cc. of air before a manometric reading was made, when the pressure was +5. After 750 cc. was removed the pressure was neutral, and the patient gradually breathed normally, and evidence of shock subsided. The following day a needle was inserted and the manometric reading was −3 to 0. The operator considered further removal of air unnecessary. This patient had no further evidence of embarrassment, lived one year and one week, and died of other tuberculous complications.

Case 3: J. B. C., reg. no. 9,240. Admitted September 24, 1924. Diagnosed calculi, multiple, both kidneys; pyonephrosis, right kidney; and later tuberculosis, pulmonary, advanced, active, on basis of findings after the lung collapse. On October 9, 1924, nephrolithotomy, left, was performed and one large and several small stones were removed. The hemorrhage was considerable during the operation. Later in the day blood transfusion was done, 600 cc. of blood being furnished by a healthy employee. The patient rallied following the transfusion.

On October 11, the patient developed considerable cough and complained of "sticking pains" in the right lower axillary region. On October 13, the patient had become very restless, and the pain in the chest was worse. The respiratory rate had markedly increased, finally becoming 80 per minute; cyanosis was marked. There were may pleural rubs heard over the right lung while over the left the excursion was diminished, and there was increased resonance and no breath-sounds over the whole lung. An X-ray of chest was made showing complete collapse of the left lung, and marked displacement of the heart and mediastinum to the right, and the diaphragm downward. I was called in consultation and found the patient in collapse, as elsewhere described. Deflation was at once arranged. The manometric readings were +2.5 to +3 before any air was removed. Readings were made following the removal of every 200 cc. of air, until by the end of thirty minutes 1800 cc. of air had been removed, and the pressure had gradually changed to −5, −2.5. The patient recovered from symptoms of shock as the air was removed, and respiration dropped from 80 to 30 per minute. The X-ray taken just after deflation showed one-half expansion of this lung, and the mediastinum and heart partially returned to normal position. The patient was resting fairly well. There was some cough and expectoration. The laboratory report for the first time showed a positive sputum on the 15th, and was positive again on the 16th and 17th, but no further positives were recorded.

An X-ray of October 24 showed the lung almost completely expanded, mediastinum nearly in normal position, and heart in quite normal place. A peculiar finding was that the left lung appeared normal and the right showed definite evidence of disease, convincing us that the active tuberculosis had possibly been the result of the collapse of the left lung, causing markedly in-

creased function of the right and tuberculous lung. Another possibility was ventured, and that was that the pleural rupture had been from the right lung through the mediastinal pleura into the left pleural sac, and that pleural adhesions had formed about the site of the rupture, preventing a double pneumothorax. This patient was discharged against medical advice on November 25, 1924. Recent reports are to the effect that he is in California and in fair health.

Case 4: A. M. W., reg. no. 11,209, admitted January 27, 1925, with a diagnosis of tuberculosis, pulmonary, far advanced, bronchopneumonic type. This patient developed a spontaneous pneumothorax, right, February 6, which gradually was followed by a hydropneumothorax right. On February 10, the symptoms were so distressing that we decided to remove some of the air from the right pleural cavity. The manometric readings were +6 to +9 before deflation, and after the removal of 1150 cc. of air were −1 to +1. The patient was much relieved, but on February 13 again showed evidence of recurrence of air, and the X-ray showed a marked hydropneumothorax, right. We again did a deflation. The pressure was +4 to +6 at the beginning, and no definite reading could be made after 1100 cc. was removed, since fluid forming in the pleural cavity got into the needle. The patient was in a critical condition, but breathed better and was much more comfortable. On February 15, a thoracentesis was done, and 300 cc. of straw-colored fluid was removed. The patient received relief each time, but symptoms returned, and two hours after the fluid was removed he died.

Case 5: A. W. F., reg. no. 11,222, admitted January 29, 1925. Was diagnosed tuberculosis, pulmonary, far advanced C. The temperature was 102.2°F. The patient had pressure sores on both ears and hips on admission. Five days later he became delirious, and a diagnosis of tuberculous meningitis was made. On February 9, the patient had a sudden severe attack of dyspnea, pulse not palpable and respirations 60 per minute. Breath-sounds were absent in the left axilla, and the heart was greatly displaced to the right. Deflation was done. The manometric reading was −1 to 0 before any air was removed. We consider the cyanosis and critical condition as due to the marked consolidation of the right lung and less so on the left, which now further markedly embarrassed the circulation by collapse. Eleven hundred cc. of air was removed, after which the pressure was −4.25 to −3. Meningitis became more marked after this operation, and, while the respiratory symptoms were much relieved by deflation, the patient died on February 12, probably from general toxemia.

Case 6: H. G., reg. no. 11,716, admitted March 30, 1925. Diagnosed tuberculosis, pulmonary, far advanced C, with temperature 104°F. The

X-ray showed a definite partial pneumothorax involving nearly all of the upper lobe, right, the day of his admission, with pneumonic areas all over the rest of the right lung and upper lobe of the left lung. On May 6, this patient suffered another spontaneous pneumothorax, collapsing all of his right lung and displacing the heart and mediastinum to the left so much that it markedly embarrassed both the heart and left lung. The patient was in shock when deflation was begun, and though 100 cc. of air was removed the manometric readings varied from 0 to −2 and were 0, −0 at end of the operation. The patient's labored breathing was markedly relieved by the deflation, but he did not recover from the shock and died two hours later.

Case 7: D. B. (colored), reg. no. 11,992. Admitted April 28, 1925. Was diagnosed tuberculosis, pulmonary, far advanced C, with temperature average of 101°F. Brought in as stretcher case and was bedridden. On May 22, the patient had a spontaneous pneumothorax of the right chest with marked dyspnea and cyanosis. Deflation was performed. The manometric reading was +0.5 to +2.5 before air was removed. This pressure lessened as deflation continued until 2000 cc. of air was removed, when the pressure was −0.5 to +1.5. The rate of respiration dropped from 40 per minute to 28, and all symptoms of severe shock noted before the operation improved. That night, however, the symptoms partly returned, and the following day at 2.30 P.M. the patient suddenly grew worse and died fifteen minutes later. It is believed that this was a valvular type of pleural tear.

Case 8: R. S. J., reg. no. 12,355. Admitted to this hospital June 9, 1925. Was diagnosed tuberculosis, pulmonary, far advanced B, but the disease spread and the clinical condition became worse, so that he was classed as a C case on a second examination. On October 13, the patient had a complete collapse of the right lung, which displaced the heart and mediastinum to the left and the diaphragm and liver downward. The X-ray showed very complete or general pneumothorax, with little functioning lung in the upper left. There were extreme shock and vomiting of bile-stained fluid. The manometric reading before deflation was 0 to 0, and, after removal of 1500 cc., −2 to −0.5. The patient's condition was critical throughout the operation. There was frequent emesis, and the state of shock never passed. The patient died five hours after leaving the operating table.

SUMMARY

1. Relief of spontaneous-pneumothorax symptoms by deflation of the pleural cavity is the treatment which should be instituted as soon as symptoms call for it.

2. Deflation should be done slowly, and sufficient air should be removed to relieve the patient, but no more, especially in cases in which therapeutic collapse has been instituted.

3. The X-ray should be used, when possible, to "check up" on the conditions both before and after deflation.

4. Complete deflation is not necessary or advisable. The remaining air will absorb quickly or, in therapeutic pneumothorax, may replace a treatment.

5. Coincident, rather than resulting, rupture of the visceral pleura during artificial-pneumothorax treatment is probable in many cases.

6. Two of our eight cases treated by deflation are now alive and quite well. One other lived for over one year after deflation was performed; all but one of the eight treated were relieved of the distress of the emergency. This would justify and demand, with the results obtained here and by other operators, that the treatment be given in all cases in which the symptoms call for relief.

7. When the monometric reading is 0 to 0 at the end of the treatment, unless this is the result of fluid in the needle the prognosis is bad.

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THE VALUE OF IODINE IN INTENSIVE DOSES IN THE TREATMENT OF TUBERCULOSIS[1]

ERNEST S. MARIETTE AND JOHN W. BURKE[2]

Man has long sought for a drug which, if not specific, would at least have a marked beneficial effect upon the tuberculous process. Many drugs have been enthusiastically advocated, but without exception have, after a shorter or longer period of trial, been discarded as of little or no value. One of these drugs has been iodine, the use of which has been enthusiastically advocated in America by Ritter and in Europe by Bordeau.

We used U. S. P. tincture of iodine therapeutically at Glen Lake Sanatorium a few years ago on 14 patients for varying periods of time, lasting from two weeks to eight months. We followed very closely the method advocated by both the American and Continental writers, but with very different results. We soon noticed that, in several cases, doses above 15 mgm. were not tolerated well, producing symptoms of iodine poisoning, such as pain in the throat and epigastrium, salivation, thirst, gastroenteritis, vomiting and purging. A few even showed suppression of urination, restlessness and giddiness. Others took 30, 40 or 60 minims *t.i.d.* with no apparent discomfort.

We then decided to investigate the vehicle, the sputum, the gastric contents, the blood, the feces and the urine, of those patients taking iodine, to see in what form it was carried in the blood-stream and in what form it was excreted. If iodine circulated in the blood and tissues as iodine then a variety of combinations with the fats and proteins of the tubercle bacillus would be possible, and much could be expected from its use over long periods. If, however, it circulated as an iodide, would it be in a form which could be broken up in the body, liberating free iodine, which, in turn, could then act directly on the tuberculous process and the tubercle bacillus, as any drug must if it is going to play an important rôle in the chemotherapy of tuberculosis. The experiments recorded below, as well as the studies of pharmacologists, do not bear out this latter theory.

[1] Presented before the Minnesota Trudeau Medical Society, December 16, 1925.

[2] Glen Lake Sanatorium, Oak Terrace, Minnesota.

The Vehicle: We added 150 min. of the tincture of iodine to a glass of milk, which according to the American writers is the best vehicle. This was tested from time to time for free iodine, and none was found after three hours. Therefore, all of the free iodine must have combined with the milk protein and fat and would have to be broken up by the body before any benefit can be expected from its use.

Sputum: After the first expectoration following medication, fractional examinations of the sputum for iodine were negative, thus indicating that the saliva became mixed with the iodine only at the time of medication and that only the mouth sputum was affected.

Gastric Contents: A dog was fed 30 and 60 minims of iodine, and his stomach was pumped out 10, 20 and 30 minutes afterward. Gastric analysis showed a total absence of hydrochloric acid and no free iodine. The iodine was found only in the form of iodide and hydriodic acid. The method used for determining the presence or absence of free iodine was as follows: The liquid material was acidified with nitric acid to set free the iodine which, on addition of carbon disulphide, gave a violet color.

The Blood: Repeated examinations of the blood, both of the dog and the human being, revealed the presence of iodides but no iodine.

Sollman reports that Boehm and Berg in 1876 credited Magendie in 1852 with the discovery that serum and all protein solutions, also urine, interfere with tests for free iodine unless this is in large excess. This is due to the binding of iodine by the aromatic group of proteins and phenols and other constituents of the urine. In 1917 Sollman also reported that free iodine was not found in the blood but that iodine circulated as iodide.

The normal iodide content of human blood is 0.34–0.86 mgm. per litre. After a month's ingestion of 60 min. of tincture of iodine *t.i.d.* this was increased to 2.56 mgm. per litre.

The qualitative method for determining the iodide content of the blood-serum was as follows: Centrifuge the blood, collect the serum, wash the remaining cells a few times with tenth-normal acetic acid solution. Combine the washings with the serum. Heat serum to boiling and filter. Wash coagulum with hot water and filter. Test filtrate for iodide. The quantitative method will be described later.

Repeated examination of the feces failed to reveal iodine in any form, so further references to that part of the investigation will be omitted.

Analysis of the urine showed that most of the iodine was excreted

through this channel; not as iodine, however, but in the form of iodide and hydriodic acid.

One patient was given a single dose, 20 minims of the tincture, and fractional samples of his urine were examined. The first sample was collected in 20 minutes, and contained the bulk of the drug in its converted form. The second sample 40 minutes later contained only a small amount. The third sample collected one hour later contained only a faint trace, while the fourth sample was entirely negative. This was repeated in five days with the same results.

The use of iodine for a month or more, however, changed the excretion time, so that traces of the converted drug could be found 24 hours after the last dose and none after that.

The pure alcoholic solution was next tried, by giving a patient who had not taken iodine previously, one dose of 50 minims, and successive samples of the urine were collected. Of these, the sample collected forty hours after medication was the first to be entirely free from the iodide.

The toxic symptoms produced seemed more severe than those following the use of U. S. P. tincture. Further observation with this drug was discontinued.

The quantitative determinations of the iodide in twenty-four-hour specimens of urine and sputum were made after the method of Volhard, slightly modified by using solutions only one-tenth his strength, thus giving us a more delicate end-reaction.

Two specimens of urine 10 cc. each were prepared in 100 cc. volumetric flasks. No. 1 was treated with 10 cc. standard silver-nitrate solution (2.9075 gm. silver nitrate per 1,000 cc.), 1 cc. of which corresponds to 0.001 gm. sodium chloride. To this, 1 cc. of nitric acid and 1 cc. of saturated solution of ferric ammonium sulphate were added, and the urine titrated with standard potassium-sulphocyanate solution. The results thus obtained represented sodium chloride and sodium iodide.

No. 2 was treated with nitric acid, and the iodine extracted by means of carbon disulphide. The urine freed from carbon disulphide was titrated for chlorides as in sample no. 1. This gives sodium chloride only, and by subtracting the results of nos. 2 and 1 the amount of sodium iodide is obtained.

These tests were made on the same patients, so results from the urine and sputum have been tabulated together. The results of this tabulation show that most, but not all, of the iodine has been accounted for.

No attempt has been made to explain what has happened to the iodine which was unaccounted for.

INTAKE IODINE IN GRAMS	OUTPUT					
	Urine				Sputum	
	Urine, cc.	Total sodium chloride and sodium iodide	Sodium chloride	Sodium iodide	cc.	Iodide output in grams
2.598	1,200	8.76	6.203	2.557	42	0.039
2.598	700	6.58	4.112	2.458	60	0.0987
2.598	1,420	9.656	7.325	2.331	35	0.1003
2.598	1,050	0.030	6.732	2.298	98	0.192
2.598	600	5.52	3.211	2.309	35	0.101

INTAKE IN GRAMS	OUTPUT IN GRAMS	UNACCOUNTED FOR IN GRAMS
2.598	2.596	0.002
2.598	2.556	0.042
2.598	2.558	0.040
2.598	2.553	0.045
2.598	2.510	0.088

SUMMARY

According to Ritter iodine is nontoxic, nonirritant and noncaustic. We found, however, that iodine is toxic, irritant and caustic; nearly as caustic as 10 per cent sodium hydroxide.

It is also claimed by Ritter that "Iodine modified or in combination with the various proteins possesses no advantage over the ordinary tincture when given in milk." This is true because milk fat and protein completely bind the iodine of the tincture, converting it into iodide.

Our experiments confirmed the work of Sollman, in so far as he states that iodine circulates in the blood and tissues only as an iodide and, as such, is excreted in the urine.

The question then arises whether these iodides can be converted in the human body into free iodine, which would then combine directly with the protein and fats of the tubercle bacillus. This, it seems to us, is the crux of iodine therapy. If it does not, and continues to circulate as an iodide, how much harm does an iodide do to a tuberculous process?

According to Ritter, organic iodine preparations are all changed in the bodily economy, the free iodine being liberated from its molecules. This does not agree with the findings of Sollman, who reports that the

blood, which after the administration of free iodine contains an iodide, cannot liberate the iodine on acidulation because the iodine is bound through the protein and not the alkali. "Free iodine cannot be liberated anywhere in the body since all conceivable reactions for the liberation of iodine from its compounds require a much higher hydrogen-ion concentration than exists anywhere in the body" (Sollman). This is to our mind the pivotal point of iodine therapy, and discredits it completely.

Clinically, our results were very disappointing. None of our patients showed any improvement other than was to be expected in ordinary sanatorium treatment. Some of the cases were failing before iodine was given and the course of their disease was unchanged.

CONCLUSIONS

Clinically, no beneficial results were observed. From our experiments and those of others we conclude that, as iodine circulates in the blood only as an iodide and, as such, is rapidly eliminated, and, as such, cannot be converted in the body into free iodine, therefore it is impossible to saturate the body with iodine and thereby inhibit bacterial growth. Therefore, in our opinion the tincture of iodine used in intensive doses is of no value in the treatment of tuberculosis in any form and may be of definite harm because iodine circulates as an iodide.

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THE TECHNIQUE OF THE RED CELL SEDIMENTATION REACTION[1]

ALF WESTERGREN[2]

If blood is prevented from coagulating, the red blood corpuscles form aggregates, and settle down with a different velocity in different physiological and pathological conditions. An increased speed of sedimentation is, above all, caused by an increase of the plasma globulins, but very likely other factors also affect the suspension stability of the blood.

If the sedimentation reaction (*SR*) is carried out as detailed in the following pages, and if simply the *sedimentation in one hour* is regarded, the following *standard values* have been obtained: *In men:* normal 1–3 mm.; border-line figures 4–7 mm. *In women:* normal (1–)4–7 mm.; border-line figures 8–11 mm. (In children, broadly speaking, the same standard can be applied as in women.) As slightly pathological can be regarded figures of (4–)8–11 mm. in men, and (8–)12–15 mm. in women. Figures above 30–35 mm. must be counted as a strong reaction; not infrequently, however, values exceeding 100 mm. in one hour are obtained. A physiological increase of the speed of sedimentation is chiefly found in pregnant women.

As a rule, the reaction can be regarded as reflecting the intensity of exudative inflammation (or of destructive processes). A pathological *SR* value, however, may occur in nearly all sorts of diseases, the test being in this respect rather like fever and leucocytosis; for instance, the highest figures (above 100 mm.) are found in such conditions as lobar pneumonia, rheumatic polyarthritis, certain forms of nephritis, etc. In uncomplicated cases of tuberculosis the figures rather seldom exceed 100 mm. A normal reaction is, of course, met with in all sorts of functional diseases, but a normal *SR* does not at all exclude an organic disease, such a value also being frequently found in most organic nervous diseases, digestive disorders, arthropathia deformans, etc.

An *inhibiting* influence on the sedimentation is especially exercised by

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cardiac decompensation. In certain forms of liver disease and in severe cachexia, a relatively reduced *SR* figure can also be observed. In *anaemia* special factors causing an increase or decrease of the sedimentation are active; from a practical point of view, however, their influence can, almost as a rule, be disregarded.

More and more, the *SR* has been accepted as an important clinical reaction, for the present especially with regard to the prognosis of tuber-

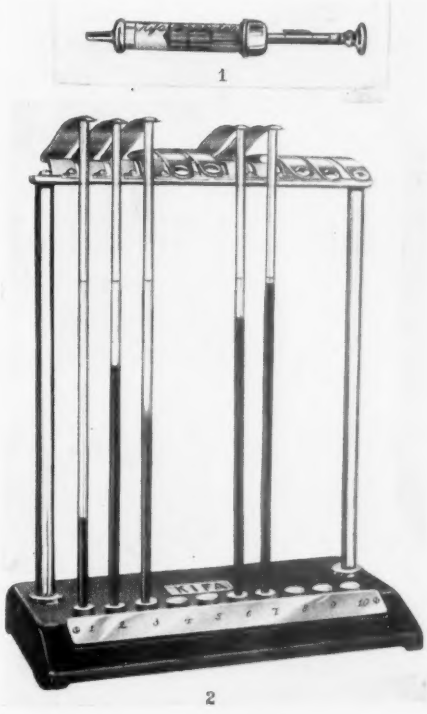

FIG. 1. SYRINGE WITH STOP-BAR ARRANGEMENT
FIG. 2. STAND WITH TESTS

culosis. Low figures, and particularly normal values, point to a good prognosis; high figures indicate a greater intensity of the pathological processes. By repeating the test, at intervals of days, weeks or months, a conception of the progress of the disease is obtained, which is, as a rule, more valuable than that given by the body temperature.

Concerning further theoretical and practical clinical facts of the reaction and the principles of testing the sedimentation rate (including full

description of the instruments required) reference is made to a more detailed article by the author (1). A warning must be given here against so called micro methods. Some authors use only 1 cc. of blood and capillary tubes, but careful investigations have shown that the results of such methods are too unreliable, especially in cases with a total cell volume that is not reduced and with a strong tendency to clumping.

According to the following method, about 1 cc. of blood is taken with a particular syringe (fig. 1) holding the exact quantity of sodium-citrate solution to get a mixture of 80 per cent blood and 20 per cent citrate solution. For testing the sedimentation rate pipette tubes are used, of 300 mm. length and about 2.5 mm. internal diameter, with a very short point. The blood is sucked up to *200 mm. of height* (marked; the volume here is 0.9 to 1.15 cc.) and the pipette tube is placed vertically into a special stand (fig. 2). Now the time is noted, and the development of the red cell sedimentation can be observed.

The test is easily made in a minute or two; but for obtaining reliable results unsuitable or incorrect instruments must be avoided and the following instructions must be observed minutely. Unfortunately, so called Westergren's methods and instruments, which are positively imperfect to a great degree, have been pretty much employed.[3]

HOW TO PERFORM THE SEDIMENTATION TEST

1. Draw a quantity of a *sodium-citrate solution of 3.7 per cent strength* into the syringe, and adjust the piston so that the stop-bar rests against the back end of the syringe barrel. Make sure that any air bubbles formed are removed from the syringe.

2. Place the needle carefully on the syringe and puncture a suitable vein. Fill the syringe completely with blood; that is, *pull out the plunger as far as it will go, until it is stopped by the end-piece of the barrel.*

3. Empty the syringe *immediately*, with the needle remaining on it, into a storage tube. Mix the contents *at once* by turning the tube up and down a couple of times, while keeping it tightly corked, or closed with a dry finger.

4. Before the sample is to be tested for sedimentation mix contents once more by turning the tube up and down a few times. In order to improve the mixing still further, suck contents from the bottom of the

[3] Correct instruments are manufactured by Kirurgiska Instruments Fabriks Aktiebolaget (KIFA), Stockholm.

tube into the pipette and blow it back into the tube three times. When this has been done, suck enough of the contents into the pipette to reach the mark (200 mm. from the point). Place the pipette into the stand. The fluid level should now be at the mark, or, at the most, two or three millimetres from it. If the divergence is greater than this, or if too many air bubbles make it difficult to observe the level of the fluid, the pipette should be removed cautiously from the stand and its contents blown back into the storage tube. Then the pipette is filled again. Avoid unneccessary blowing and shaking of the blood.

Examination of the sample, which is to take place in *1*, *2* and *24 hours* after the pipette has been placed in the stand, consists in *measuring the height of the plasma layer*, that is, the distance from the lower meniscus of the free surface of the fluid to the line formed by the settling or settled blood corpuscles. If this border-line should be indeterminate, measure to the point where good density appears to commence (where the transparency ends). Leucocytes, etc., composing the white layer, which especially at the 24-hour examination is deposited on top of the red cells, are counted as belonging to the plasma. It is particularly in cases of severe anaemia that the border between the sediment and the clear portion is apt to be less distinct. In such cases the uncertainty may sometimes amount to 5 mm., and in sporadic instances even more. Such great divergences, however, are hardly conceivable, except when the reading has been made by unpractised persons. When the line is very indeterminate the fact should be recorded in the report by placing an x, or xx, before the figure.

The 1 and 2-hour examinations should always take place on the minute; at the 24-hour examination half an hour more or less is of no importance.

By making examinations after the lapse of one, two and twenty-four hours, one gains a knowledge of the process of sedimentation which is quite satisfactory for ordinary purposes. When feasible, these three readings should always be set down in journals or test reports. When the *SR* indication has to be expressed with only one figure (as in diagrams and summary tables), as a rule only the sedimentation after *one hour* is given. It is inadvisable, however, to restrict the examination to this one reading, because the reliability and distinctness of the reaction results are much lessened thereby.

The syringe is adjusted so that the stop device will apportion 80 vol. per cent of blood and 20 per cent citrate solution. It is important for obtaining reliable reaction results that this proportion remain as un-

changed as possible. The margin of error of the syringe is about ± 1 per cent. This error is without practical importance; but greater errors may be caused by air admixture in the citrate solution and especially from leakage when the vein is punctured. Besides the constant bubble, formed by the air in the needle, not more than the same volume of further admixture of air is permissible.

Make sure before taking the test sample that the parts of the syringe are screwed up tightly, and that the plunger moves freely in the barrel. In order to clean the syringe between each test, rinse it out a few times with water and once with the citrate solution. Immediately after it has been used, clean it thoroughly, if necessary with soap water or ammonia. It is unnecessary and injurious to boil the syringe.

The needles must be joined air-tight to the point of the syringe. The needle point should be ground with a comparatively short taper. See that the needles are well cleaned, especially inside the bulb, and that the points are perfectly sharp.

Only one syringe is necessary for the test, provided a number of suitable, well-fitting needles are available. The simplest way of disinfecting the needles is to place them in a bath of alcohol-ether. Before fitting the needle on the syringe see that it is free from any liquid. (Remove the drop of citrate solution which has been formed at the point of the syringe.)

The pipettes, as well as the storing tubes, must be *perfectly clean and thoroughly dry*. They should be cleaned as soon as possible after the 24-hour examination has taken place (with alkali if necessary), and washed well with water and dried afterward by drawing spirit and ether through them.

The rubber stoppers of the stand must be well cleaned immediately after using.

The disinfection of the skin is best performed with ether, and for this purpose some rolled-up gauze is to be preferred to a piece of cotton, because the cotton-dust may foul the blood and interfere with the sedimentation process.

The puncturing of the vein and the taking of the test sample should be carried out as rapidly as possible and without any break. If necessary, apply *stasis*, but unnecessarily lengthy stasis should be avoided, especially if the sample is to be investigated in regard to number of blood corpuscles, etc.

Keeping of the blood sample: The rate of sedimentation can be deter-

mined immediately, but the blood may be kept in the storage tube up to 4–6 hours without detriment.

The room temperature during the sedimentation should be about 18°C. (16°–20°). The blood sample or the pipettes should not have been kept immediately before the test in some place where their temperature will diverge greatly from the above-mentioned room temperature, as near radiators, or exposed to direct sun-rays, or near cold windows.

Coagulation, or even a tendency towards clotting, makes it *absolutely necessary to reject the sample*, and also a plainly evident general *haemolysis*. (The latter is especially liable to occur if the syringe is emptied too violently into the storing tube.)

BLOOD TEST WITHOUT PUNCTURING OF VEIN

If a suitable vein cannot be found (for instance, as in small children) the following method may be applied:

1. Mark off 1.25 cc. volume on a storing tube and pour into the tube 1/5 (that is, 0.25 cc.) of the citrate solution. In practice, this is most simply accomplished by marking out the volume of a full syringe on the storing tube, after which the required quantity of citrate solution is measured by means of the syringe.

2. After inducing hyperaemia by means of a hot hand-bath or foot-bath, and drying and disinfecting the skin, make a rather deep incision with a knife or a lancet and collect the blood directly in the storing tube, while stirring the contents continuously. The tube must be filled rapidly up to the mark.

COUNTING BLOOD CELLS, ETC.

After the blood has been sucked up into the pipette there will remain in the storing tube about 0.5 cc. of citrated blood (or 1.5 to 0.5 cc. if a bigger model of syringe is used). This portion of blood may be used for counting blood cells, or determining haemoglobin, nonprotein nitrogen, blood-sugar, etc. (Folin methods), and yet other investigations, but for this purpose the puncturing of the vein must have been carried out without, or with *extremely brief, stasis*. The blood may very well be kept some time before such an investigation takes place.

With reference to the sedimentation tendency of the blood corpuscles it must be noted that the citrated blood is well mixed before it is added to the dilution fluid. The storing tube must consequently first be *thoroughly shaken* (not merely turned up and down), whereupon further

mixing is accomplished by alternate sucking and blowing with the measuring pipette.

In counting white blood cells it must be noted that the acetic-acid content of the diluting fluid should be increased to 5 per cent. For the rest, the counting of blood corpuscles and determination of haemoglobin content are carried out according to the usual methods, but the figures obtained must finally be multiplied by 1.25 (corresponding to the dilution with citrate solution in the syringe).

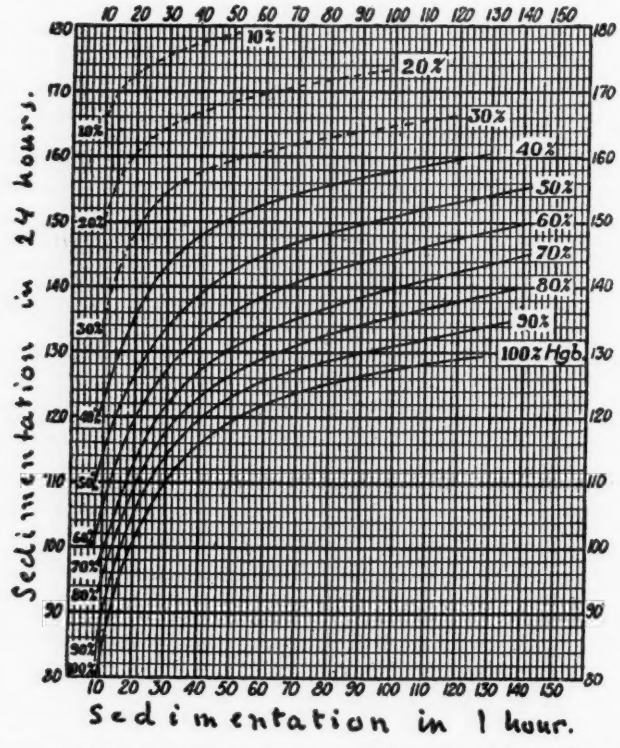

FIG. 3. DIAGRAM TO SHOW RELATION BETWEEN THE SEDIMENTATION IN 1 AND 24 HOURS AND THE HAEMOGLOBIN CONTENT OF THE BLOOD

DETERMINATION OF THE HAEMOGLOBIN DIRECT FROM THE *SR* FIGURES

The relation between the sedimentation figures at 1 hour and 24 hours is chiefly influenced by the haemoglobin content of the blood (the total cell volume). With the aid of the diagram an estimation of the haemoglobin content in the blood sample may be obtained as a supplementary

product. If, for example, one certain test sample of blood after 1 hour has settled *75* mm., and after 24 hours *139* mm., it will be seen from the diagram (fig. 3) that the haemoglobin content is in this case about *65 per cent.* The error in estimating haemoglobin in this way is in general not greater than 10 per cent of haemoglobin.

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A COMPARISON OF THE SCHULTE-TIGGES AND ZIEHL-NEELSEN METHODS FOR STAINING ACID-FAST BACTERIA[1,2]

JAMES S. SIMMONS AND ERNEST J. STEVES

One of the most important aids in the laboratory diagnosis of tuberculosis is the demonstration of tubercle bacilli in smears of pathological materials by means of some method of differential staining. Because of the slowness with which tubercle bacilli grow and because of various technical difficulties, cultural methods are rarely used for their identification, while the inoculation of susceptible animals with tuberculous materials for diagnostic purposes is usually resorted to only when the microörganisms are not demonstrable microscopically in stained preparations. Since so much diagnostic importance is placed on the finding of tubercle bacilli in smears, it is desirable to use a reliable technique for staining them.

Due possibly to their waxy nature, or to the low degree of permeability of their bacterial envelopes, tubercle bacilli cannot be stained easily, but when once stained they are quite resistant to the action of decolorizing agents. As mineral acids have been used most commonly as decolorizers, this property is called "acid-fastness." The terms "alkali-fastness" and "alcohol-fastness" have also been used to indicate resistance to the decolorizing action of alkalies or alcohol.

During the past 40 years a large number of methods and modifications of methods for staining tubercle bacilli have been proposed. Different dyes, decolorizing agents, and counterstains have been advocated with variations of one or more steps in the technique. While the majority of these methods can be used for the identification of acid-fast bacilli, the Ziehl-Neelsen method (1) (2) has been found most satisfactory for routine work. This procedure is so universally used and recommended that it may be considered as a standard staining method.

It has been claimed recently that the so called Schulte-Tigges method

[1] From the Laboratory Service, Fitzsimons General Hospital, Denver, Colorado, and the Department of Laboratories, Army Medical School, Washington, D. C.

[2] Published by permission of the Surgeon-General, U. S. Army.

(3), in which sodium sulphite is used for decolorization and picric acid for counterstaining, is to be preferred for the staining of tubercle bacilli. Schaub (4) reported the examination of about 800 specimens of sputum, 183 of which were positive for tubercle bacilli with the Ziehl-Neelsen stain and 244 with the Schulte-Tigges stain; and concluded that the latter was easier to perform, exposed over five times as many micro-organisms and gave 33 per cent more positives. Mills and Kendrick (5), after the examination of 70 specimens of sputum, concluded that the two methods gave the same number of positive specimens; and that the Schulte-Tigges method did not have sufficient advantage over the Ziehl-Neelsen to warrant a change in the routine procedure used in their laboratories. Hasseltine and Gorman (6) examined stained preparations from the skin and nasal lesions of 100 lepers, and found the Ziehl-Neelsen method preferable to the Schulte-Tigges for routine examinations of *B. leprae*.

In our investigation comparative examinations were made of specimens of sputum from five hundred tuberculous patients, using both the Schulte-Tigges and Ziehl-Neelsen methods.

TECHNIQUE

A selected portion of each specimen of sputum was rubbed between glass slides in order to make two smears as nearly alike as possible. The smeared sputum was then dried and fixed on the slides by heat, after which one smear was stained by the Schulte-Tigges and the other by the Ziehl-Neelsen method. The technique given by Schaub (4) was followed in order to obtain comparative results.

Ziehl-Neelsen Stain: The fixed smears were stained with steaming Ziehl's carbol-fuchsin for five minutes. After washing off the excess with tap-water, the smears were decolorized with 1 per cent hydrochloric acid in 70 per cent alcohol. The smears were then washed with tap-water and counterstained with a saturated aqueous solution of methylene blue, after which they were again washed with tap-water, dried and examined.

Schulte-Tigges Stain: Fixed smears were stained with steaming Ziehl's carbol-fuchsin for one minute. All excess stain was washed off with tap-water and the smears were decolorized with a fresh 10 per cent aqueous solution of sodium sulphite. The smears were then washed with tap-water and counterstained with a saturated aqueous solution

of picric acid, after which they were again washed with tap-water, dried and examined.

Counts were made of the total number of tubercle bacilli in ten microscopic fields on each slide.

RESULTS

No tubercle bacilli were found in 35 (7 per cent) of the specimens, using either stain, while they were demonstrated in 432 (86.4 per cent) specimens with both methods. Twenty-one specimens (4.2 per cent) were found positive only by the Schulte-Tigges method and 12 (2.4 per cent) were positive only with the Ziehl-Neelsen stain.

TABLE 1

Tubercle bacilli demonstrated in 500 specimens of sputum stained by the Ziehl-Neelsen and Schulte-Tigges methods

STAINED BY ZIEHL-NEELSON METHOD	STAINED BY SCHULTE-TIGGES METHOD	SPECIMENS OF SPUTUM	
		Number	Per cent
−	−	35	7
−	+ (104 bacilli)	21	4.2
+ (81 bacilli)	−	12	2.4
+ (28,267 bacilli)	+ (28,919 bacilli)	432	86.4
Total 28,358 bacilli	Total 29,123 bacilli	500	100

− = tubercle bacilli not found; + tubercle bacilli present.

Using the Schulte-Tigges stain, 9, or 1.8 per cent, more positive specimens were found than with the Ziehl-Neelsen method.

The total number of tubercle bacilli counted in the 500 specimens stained by the Ziehl-Neelsen method was 28,358; while 29,123, or 2.6 per cent more, microörganisms were seen in the Schulte-Tigges preparations. The differences between these results are probably no greater than would have been obtained had a single staining method been used in preparing the two sets of slides, and are not considered significant.

Staining of Acid-Fast Bacteria from Cultures: The two methods were found to be of equal value for staining microörganisms from pure cultures of human, bovine and avain tubercle bacilli, six strains of so called lepra bacilli and a number of saprophytic acid-fast bacteria, including smegma bacilli, dung bacilli, hay bacilli and butter bacilli.

SUMMARY AND CONCLUSION

1. Specimens of sputum from 500 tuberculous patients were stained by both the Schulte-Tigges and Ziehl-Neelsen methods and examined for tubercle bacilli.

2. With the Schulte-Tigges method 1.8 per cent more positive specimens were found, and 2.6 per cent more tubercle bacilli were counted. These apparent advantages were probably due to accidental variations in the distribution of tubercle bacilli on the slides, and are not considered significant.

3. The two staining methods were of equal value for staining human, bovine and avian tubercle bacilli, lepra bacilli and a number of saprophytic acid-fast microörganisms from pure cultures.

4. It is concluded that for the differential staining of tubercle bacilli the Schulte-Tigges and Ziehl-Neelsen methods are equally valuable.

The authors were assisted in this work by Mr. Robert Whipple.

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ABSCESS OF THE LUNG[1]

S. U. MARIETTA[2]

Although tuberculosis is a most frequent cause of lung abscess, the form arising in this condition is not included in the following discussion. In passing it may be remarked, however, that certain writers have recently advocated the treatment of large, single, tuberculous abscesses by incision and drainage, a more radical procedure in the presence of tuberculous infection, it would seem, than the more usual measures, artificial pneumothorax and thoracoplasty, or some of its modifications.

According to Hartwell and Dudley, "An abscess of the lung is a focus of suppuration within the lung substance and must be differentiated from suppuration confined within the lumen of the bronchial tree, such as putrid bronchitis and bronchiectasis. It is of necessity accompanied by a destruction of lung tissue and a necrosis and bacterial liquefaction of this tissue must take place."

The condition is not too common. Nine hundred and eighty cases of acute pulmonary infection at the Hospital of the Rockefeller Institute, 1914 to 1919, showed 9 pulmonary abscesses. Six thousand autopsies at Bellevue (all diseases) showed 150 lung abscesses, less than one-third being large enough to give signs. A study of 3,250 patients at the Saskatchewan Sanatorium revealed lung abscess in 32, or 1 per cent; 4 of these being acute and 28 chronic, with an average duration of over four years. Greer cites 33 cases occurring in his practice and at the Baptist Hospital and St. Joseph's Infirmary in the last five years. He thinks that the incidence of the condition has been on the increase for the last decade, probably due, in part, to the greater frequency of nose and throat operations under general anaesthesia. There have been 17 cases at this hospital (Fort Sam Houston) during the period from October 1, 1923, to February 1, 1926 (twenty-eight months), among a total of 10,570 patients, including all types of disease, admitted to the Medical Service during that period.

[1] Published with permission of the Surgeon-General, U. S. Army, who is not responsible for any opinion expressed or conclusions reached herein.

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Lung abscesses are always secondary; that is, with few exceptions, suppuration does not occur primarily in the lung. Therefore, the exciting factor is the lodgment at some point in the pulmonary tissue of infectious material, or the implantation of certain pus-producing microorganisms in areas of pulmonary tissue where the resistance has already been lowered by disease, injury or circulatory disturbances. The etiological conditions may be variously classified, but that of Hartwell and Dudley is suggested as being at once simple, concise and easily remembered. It is as follows: 1. Those infecting microörganisms gaining entrance to the lung substance from within the lumina of the bronchi. This is subdivided into the infections involving the respiratory mucosa (lobar pneumonia, bronchopneumonia, influenza, etc.), and infection through the aspiration of foreign bodies, either by infection carried by the foreign bodies causing pneumonia and secondary abscess or by aspiration of pyogenic microörganisms without gross foreign material, the abscess arising without a preceding pneumonic process. 2. Infection from without the lumina of the bronchi, including (a) infection carried by the blood-stream (septic emboli, infarcts from emboli, pyemia), (b) infection through the lymphatic system (ulcerating esophageal carcinoma, suppurating mediastinal lymph nodes, sacculated or interlobar empyema), (c) infection through extension of a neighboring suppurative process (an empyema rupturing into a bronchus, from mediastinal suppuration, from subdiaphragmatic abscess), and (d) infection through penetrating wounds.

Other diseases than the pneumonias and influenza may be causative factors. Jermain mentions different fungi, echinococcus, *B. mallei* and the *Spirocheta pallida* as possible exciting agents. The pus cocci, particularly the *Staphylococcus aureus*, are most frequently found, and may be associated with pneumococci or the influenza bacillus. Greer found the *Staphylococcus aureus* to be the predominating microörganism in the sputum in his cases, but the infection is usually of a mixed type with the streptococcus or staphylococcus predominating. As a matter of fact lobar pneumonia is one of the least frequent causes of abscess of the lung. Of 770 cases of lobar pneumonia at the Hospital of the Rockefeller Institute, only two had abscess. Hartwell and Dudley report Musser and Norris's statistics of 76 clinical cases of lung abscess in 12,030 cases of lobar pneumonia, and 28 lung abscesses in 1,294 autopsies on lobar-pneumonia cases. Jermain mentions Fraenkel's series of 1,200 cases of lobar pneumonia with a 2 per cent incidence of abscess. Chronic

alcoholism, diabetes or enfeeblement from any cause are predisposing factors. A well-developed abscess may appear early, within ten days of the onset of the illness, or only after several weeks or months. With bronchopneumonia, the aspiration of infectious material into the finer bronchi, abetted by enfeeblement due to old age, malnutrition, etc., may produce abscess.

Of all the causes the aspiration of infectious material during an operation on the upper respiratory tract under a general anaesthetic, especially tonsillectomy, ranks first (Greene). Aspiration may similarly occur in cases of unconsciousness from any cause, in alcoholism, or insanity; or articles, such as pins, tacks, pieces of straw, etc., being held in the mouth, may be aspirated accidentally. Infectious material may be aspirated from a diseased area to a healthy portion of the lung or to the other lung, as in suppurative bronchitis, bronchiectasis or abscess, there setting up a new process.

Jermain mentions infected emboli as being the most frequent cause of abscess. These may arise from any focus of suppuration in the body, close or distant.

Perforating gunshot wounds or penetrating stab wounds rarely cause abscess, unless foreign infectious material, such as pieces of clothing, are carried into the lung tissue. Laceration of the lung tissue from trauma, as in certain cases of fracture of the ribs, with secondary infection from the bronchi, will explain some cases.

For the purpose of study, abscesses may be variously classified, as to the etiological factor, as to the type of microörganism present, as to location, that is, the lobe of the lung involved, whether single or multiple and whether acute or chronic.

The various etiological factors and the types of microörganism responsible have been discussed above. It is generally considered that abscesses are more frequent in the lower lobes, but Hartwell and Dudley found about the same proportion in the upper and lower lobes. Greer noted a predilection for the lower lobes, notably the right lower, especially in the postoperative cases. Of the 15 cases of single abscess in this report, 11, or 73.2 per cent, were in the lower portion of the lungs, 6 on the right and 5 on the left side. Stevens in his book mentions the right lower lobe as the one most frequently affected. There is an anatomical basis for the more frequent lodgment of aspirated matter in the right lower lobe. The right main bronchus is wider, shorter and more vertical than the left, forming an angle to the median plane of about 29 degrees as

compared with 46 degrees for the left main bronchus. Further, the septum at the bottom of the trachea, and separating the two bronchi, is to the left of the median line, the right bronchus appearing to be a more direct continuation of the trachea than the left. Abscesses arising as the result of the aspiration of foreign bodies or of infectious material, those due to trauma or wounds, those following lobar pneumonia or the extension of infection from neighboring suppurative processes, are apt to be single; those due to infection through the blood-stream (septic endocarditis, septic emboli, pyemia), through the lymphatic system or secondary to bronchopneumonia, are apt to be multiple.

The symptoms of pulmonary abscess are cough, purulent expectoration, dyspnea, intermittent or remittent temperature, possibly pain in the chest if there is pleural involvement, sweating and chills or chilly sensations, but these are frequently masked by those of the original condition. The blood picture shows a polymorphonuclear leucocytosis in the acute stage. In the chronic cases this is often not marked. The onset may be acute, the symptoms resembling pneumonia, with a chill, temperature 102° to 104°, leucocytosis 15,000 to 20,000 with an increase in the polymorphonuclears, dry cough, and possibly pain in the chest; or it may be more gradual, with general malaise, moderate fever, unproductive cough, and a gradually increasing leucocyte count. The X-ray picture at this time is not of great assistance as, though it shows the location of the pathological changes, there is nothing distinctive or characteristic of abscess. In any case, the most characteristic sign of a fully developed abscess (single type) is the sudden expectoration of a large amount of more or less offensive pus. If of the multiple type, this symptom is absent, but pain is often a more prominent symptom than with the single abscess.

If, following lobar pneumonia, there is no crisis, the temperature becomes of the septic type, there are no physical signs of resolution over the involved area, the cough increases in severity, the sputum becomes purulent and there are chilly sensations and sweating, the presence of a lung abscess is probable. The cough in lung abscess varies in degree, but it is present in all cases. In the early stage it is nonproductive and not characteristic. After rupture it is paroxysmal, and dependent upon the adequacy of the drainage. Changes of position bring about a paroxysm of coughing with profuse expectoration. The sputum shows nothing distinctive before rupture of the abscess. At the time of rupture it is copious, purulent and may contain blood. In fact, there may

be a definite hemoptysis. With regard to the offensiveness of the sputum, Jermain is the only author noted who intimates that it does not have this characteristic. He states that it is not offensive in odor as a rule. All others mention its foul character. All of our patients have complained of the sickening taste, and most of them of the offensive odor. It is true that this varies, and is more pronounced in proportion as gangrene is present. Microscopically, the sputum contains pus and epithelial cells, elastic fibres, hematoidin crystals and microörganisms. The absence of elastic fibres, however, does not negative abscess. With adequate drainage the sputum decreases, and finally ceases. If there are multiple foci, even the raising of large amounts of pus may not be adequate, and the patient dies from sepsis. The sputum supposedly does not separate, on standing, into the three layers mentioned in many textbooks, as being distinctive of bronchiectatic sputum. As a differential diagnostic measure this is of little value and has been discarded for more exact procedures. The amount of sputum raised at the time of rupture is dependent upon the size and location of the abscess, also upon the adequacy of the drainage. With poor drainage, expectoration continues, and the condition becomes chronic. Even in this stage the amount of expectoration is not a positive indication of the size of the abscess or of the degree of drainage, as a purulent inflammation of the bronchial mucosa may be present, causing of itself a certain amount of expectoration.

Dyspnea is dependent both upon the degree of toxicity present and upon the amount of pulmonary involvement. It is more marked in the cases of multiple abscesses, due to septic emboli or empyema.

The fever is of the septic type, and is absent only in the old chronic cases with good drainage, but still not complete enough to permit of cure. Chills and sweats are more common when gangrene is present. In the multiple type of abscesses the fever continues to the end. The height and persistence of the temperature is in direct relation to the freedom of the drainage. Pain is not a necessary symptom, its presence depending upon the degree of pleuritic involvement.

Small or large, single or multiple, the general pathological process is the same. There is a central cavity containing pus and disintegrated lung tissue; in the acute cases there is a surrounding area of pneumonic solidification, purulent, hemorrhagic, or both, outside of which, for a variable distance, the lung tissue shows congestion and edema; surrounding the cavity in chronic abscesses is a definite fibrous wall, varying in

thickness with the age of the process, the adequacy of the drainage, the resistance of the patient, etc. Pleuritic involvement is present over superficial abscesses, plastic to adhesive, as the abscess is more acute or more chronic. The abscess often ruptures into a bronchus and, if drainage is free, healing takes place with the formation of scar-tissue and the obliteration of the cavity. A superficial abscess may, however, perforate the pleura and give rise to empyema or pyopneumothorax.

The diagnosis is one of elimination. The history is of great importance. Any failure of resolution or clearing up of the pulmonary tissue following an infectious disease therein (lobar pneumonia, bronchopneumonia, influenza, etc.); symptoms indicating localized pulmonary involvement after a general anesthetic, especially when given for operative procedures on the upper respiratory tract; or in the presence of known suppurative processes elsewhere in the body, should always cause one to think of lung abscess.

Cough is always present and also purulent expectoration, more or less foul in character, as soon as communication with a bronchus is established. The septic type of the temperature and a moderate to marked leucocytosis are of assistance. The X-ray is of great value in the diagnosis, and it is absolutely necessary for the definite localization of a pulmonary abscess. Thickened pleura, if marked, or a prominent area of pneumonic reaction about an abscess may vitiate the information to be obtained in this way. The plates should be stereoscopic and, as the definite localization of the condition may be the deciding factor in the method of treatment to be followed, it is advisable to take both anterior-posterior and lateral views. Ferguson says that the judicious use of sedatives for 24 to 48 hours preceding examination by X-ray is helpful, as there is an accumulation of secretions and thus exaggeration of the signs. The physical signs are not very characteristic, only serving, as a rule, to show the presence of a localized area of involvement in the lung. Further, the physical signs may be masked by those of the preceding disease. If there is a cavity of considerable size, signs of this may be elicited, varying with the amount of its contents. The symptoms and signs of the small, embolic abscesses are quite indefinite, and the condition often cannot be diagnosed positively. One may get small patches of pleural friction, with cough, fever and a small amount of fetid expectoration, the physical signs not being definite enough to differeniate from the original condition. There may be signs of scattered areas of consolidation and of moisture.

A closed abscess may show only percussion changes and possibly those due to compression. In the well-developed single abscess we usually find diminished expansion on the affected side, with diminished tactile fremitus over the involved area. Percussion gives localized dulness, more marked in the centre and shading out to a surrounding normal or increased resonance. This is less definite as the abscess is deeper in the lung tissue. The breath-sounds are decreased over the abscess early, but, with more intense consolidation or the formation of a fair-sized cavity, they will become bronchial or cavernous. Expiration is usually prolonged in the contiguous lung tissue. Moist râles, dependent in size, number, and character upon the stage of the process, are present, especially after cough.

The use of the bronchoscope is advocated by some as a means of diagnosis, but its use had best be left to those special clinics where an expert in its use is present. Exploratory chest puncture is another diagnostic procedure highly recommended by some authors. Hartwell and Dudley state that it should be employed when abscess is suspected. They advise the use of a needle of large calibre, and more than one puncture if necessary for exploration. They admit the danger of infecting the pleural cavity, but state that pleural adhesions may be present and furnish protection, and if not present the puncture itself may cause adhesions. The puncture serves to differentiate pyothorax, or pyopneumothorax, from abscess by the depth at which the pus is reached, but the obtaining of a few drops of pus is not a positive indication of abscess, as unresolved pneumonia may yield such findings; further, the failure to obtain pus at a given time is not positive proof that an abscess is not present, as a later puncture may show positive findings. Hartwell and Dudley quote Quincke and Picot as condemning the procedure and reporting six cases of empyema and severe cellulitis of the chest wall, with three deaths, following it. Head recommends puncture, saying that a needle should be plunged into the affected area at as many different points as necessary to locate the focus and establish the diagnosis. Greene also apparently favors its use if localized dulness can be determined. Jermain considers puncture as seldom justifiable as a means of diagnosis, not harmful if the pleural surfaces are adherent, but dangerous otherwise. Hedblom considers aspiration for localization of an abscess, without preliminary thoracotomy to prevent infection of the pleural cavity, as unjustifiable. Ferguson thinks that exploratory pulmonary puncture and bismuth injection are helpful in differentiating abscess and bron-

chiectasis, or in demonstrating an abscess in a localized infiltrated area. He considers it especially important in order to determine the appropriate treatment. Greer feels that needling of the abscess is dangerous because of the danger of infecting the pleural cavity. He advises the use of an artificial-pneumothorax apparatus to determine the presence of adhesions and their extent, by repeatedly inserting the needle in all directions peripherally from the centre. In the writer's opinion the needle should never be used without the precautionary measures which Greer mentions, as the production of an empyema is otherwise very probable and the presence of such a complication, aside from its extreme seriousness, interferes with the further proper treatment of the abscess.

The diagnosis of lung abscess necessitates a differential diagnosis from bronchiectasis, gangrene, encysted empyema, pulmonary tuberculosis and lung tumors.

Bronchiectasis may be very difficult or impossible to differentiate from abscess. The onset of the disease is more gradual in the former condition, and the septic manifestations are fewer. The sputum is more abundant, apt to be more foul, contains no elastic fibres, and the cough and expectoration are more affected by change in posture. It is not unusual in these cases to see a gush of thin, foul pus escape from the mouth and nose following a rather mild paroxysm of coughing. The periodicity of the expectoration is more marked. There is slight or no leucocytosis. The patients may appear to be in good physical condition, but the same is true of the chronic cases of lung abscess with good drainage. There seems to be less tendency to temperature elevation in bronchiectasis. The X-ray may show the dilated bronchi instead of a local collection of fluid and air as in abscess.

In gangrene we have the expectoration of small amounts of reddish or brownish extremely fetid material, as compared with the expectoration in abscess of considerable amounts of purulent and less offensive sputum. Also, there is usually present in the sputum of gangrene shreds or fragments of gangrenous lung tissue. The septic manifestations and prostration are more marked in gangrene.

Encysted empyema may follow the pneumonias, influenza, injury, etc., as does abscess. The area of percussion dulness is usually more sharply delimited than is found in abscess; the early signs and symptoms are usually more pronounced; if the empyema does not rupture into the lung there is little sputum; if it does so rupture, signs of pyopneumothorax appear. Again stereoscopic X-ray plates are of the greatest assistance.

Head mentions that many patients with chronic abscess of the lung are up and about, run a continuous elevation of temperature, and have a persistent, harassing cough, paroxysmal in nature, over long periods of time, and that these symptoms naturally lead to the thought of the commoner tuberculous condition. This is true, but the differential diagnosis, except in the early stage, is not too difficult, even with an abscess of the upper lobe. Head advises the use of the exploratory needle, which is not believed by the writer to be justifiable unless the needle is attached to the manometer of an artificial-pneumothorax apparatus, and the lung not entered unless pleural adhesions are present. He also mentions tuberculin, stating that a case of persistent, harassing cough, with fever, reacting negatively to tuberculin, calls for serious consideration as lung abscess. It would seem that with the well-known large percentage of all adults reacting positively to tuberculin, a case of abscess might easily give a positive reaction and, if the test be given great consideration, lead to an erroneous diagnosis. The previous history here is of great importance, more especially as it refers to one of the etiological factors for abscess. An abscess is usually in the lower lobe, while tuberculosis is in the upper lobe or perhaps extending out from the hilum region. The physical signs, of themselves, will not differentiate, and may be quite similar in the two conditions, except that in abscess they are apt to be more circumscribed and well defined than in a tuberculous lesion. The sputum in lung abscess is more purulent and more apt to be offensive, and is negative for tubercle bacilli. It is more abundant than for a tuberculous lesion of similar extent, and is more affected by change of position. Also, we have a history of the sudden raising of a large amount of pus at the time of rupture into a bronchus. There is a polymorphonuclear leucocytosis in abscess and a normal or decreased white count in tuberculosis. Finally, the careful study of stereoscopic X-ray plates is of the utmost value in the differentiation of the two conditions.

Lung tumors may be differentiated by a careful history, the difference in the character of the sputum, and the study of stereoscopic X-ray plates; also by the discovery, possibly, of a primary lesion elsewhere in the body.

The possible complications of lung abscess are empyema, pyopneumothorax, purulent pericarditis, aspiration pneumonia, hemorrhage, metastatic abscesses of the brain, liver, spleen or kidneys, and gangrene.

The prognosis depends upon the type of the infection, the location of the abscess, the general condition of the patient, the method of treatment

employed, and the occurrence and type of complications. Cases which recover spontaneously through bronchial drainage may have a recurrence. The prognosis is said to be better in the upper lobe cases because of the better drainage. Multiple abscesses are nearly always fatal. Gangrene is a very serious complication. The mortality rate given by different writers varies from 20 per cent to 60 per cent, according to the type of the abscess and the method of treatment employed. The operative rate is lower than in any other method of treatment. Scudder reports 33 per cent, Tewksbury 30 per cent, and Sauerbruch 20 per cent in one series and 35 per cent in another. Lenhartz had 18.5 per cent mortality in 182 operated cases. Greer reported 25 per cent of deaths in eight operated. His total mortality for all cases, irrespective of the method of treatment, was 36.3 per cent. In cases given medical treatment only, supposedly including postural drainage, Tewksbury had 60 per cent of deaths and Greer 30 per cent (13 cases). Greer had used postural drainage in all his cases. The latter also reports 50 per cent mortality in 12 cases treated by artificial pneumothorax. Whittemore considers 10 to 30 per cent of cases curable by expectant treatment, a small number by artificial pneumothorax, and a limited number by the use of the bronchoscope, if the treatment is instituted early. His mortality in 100 cases treated by surgery was 18. At the Mayo Clinic in 1923, 46 cases of chronic lung abscess were treated with 9 deaths, a mortality of 20 per cent. The latter is reported by Graham, but he does not mention the method of treatment employed; supposedly it was surgical in all cases. He further states that autopsy showed multiple abscesses or bronchiectasis in the fatal cases.

Before taking up the treatment of abscess something should be said as to the prophylaxis. The only etiological factors that can be guarded against practically are the different operative procedures which may be done about the upper respiratory tract, including the extraction of teeth, in which event there is a probable choice as to general or local anaesthesia. The aspiration of infectious material while under general anaesthesia for such operations is a prolific cause of lung abscesses, and the use of local anaesthetics, whenever it is at all possible, will lower their incidence. It is stated also that early drainage of empyema is a prophylactic measure in the prevention of extension, in some cases, of infection from the pleura into the lung.

The treatment may be divided into the medical or expectant treatment and the surgical. The latter includes incision and drainage, extrapleural

thoracoplasty, lobectomy, artificial pneumothorax and the use of the bronchoscope.

Medical treatment is the indicated treatment in the early and acute stage of all abscesses of the lung. Not infrequently, healing takes place by rupture into the bronchus and the establishment of adequate drainage. Anticipatory to such rupture, rest in bed and supporting measures are the rule. Sedatives for cough are sometimes advisable, but much medication is to be avoided. Immediately following the rupture, postural drainage should be instituted to assist that already provided by nature. It is believed that failure in this method of treatment not infrequently occurs as the result of the patient not being placed in the position best calculated to assist drainage, not using it frequently enough or for long enough periods. Ordinarily, and if the patient's condition is not such as to contraindicate it, the best results are obtained by the patient lying across the bed, face down, with the groins at the edge of the bed, so that, as the body is bent over, the head is on the floor, with the body vertical. The weight may be partially supported by the hands at the sides of the head. A pus-basin is placed on the floor at the head, and this position is held for at least five minutes three times a day, in the early morning, before lunch, and at bedtime. If drainage is slow or is better promoted by a longer period, the treatment should last for ten minutes, and most patients do not find this too difficult after they become somewhat accustomed to it. This drainage is not a matter that can be left to the patient; it must be supervised, and the patient encouraged in its use. In certain cases, and dependent upon the position of the abscess, the drainage is further facilitated by having the patient lie for a few minutes on the sound side before assuming the drainage position. If continuous improvement, as evidenced by the gradual lowering of the temperature to normal, decrease in the amount and offensiveness of the sputum, decrease in the white blood count, improvement in the appetite and the general condition, less cough, with a clearing up of the involved areas, as shown by fluoroscopy or X-ray plates, and diminution in the physical findings, takes place, the probabilities of healing by medical treatment alone are good, and it should be persisted in. Even if the patient does not show a steady improvement, as long as there is not a definitely downward course the medical treatment should be continued for a reasonable period. Hedblom says that, in all cases which do not become steadily worse during a period of from one to two months, expectant treatment is indicated. Multiple abscesses involving more than one lobe permit of

no other form of treatment. Also, when there is a marked pleural involvement from an antecedent or complicating process, preventing the localization of the abscess, expectant treatment will have to be followed, with the hope of such improvement taking place as will permit of the decision as to more definitive measures. Medical treatment does not promise much in the old chronic cases. Ferguson reports no results in the treatment by autogenous vaccines of 9 cases of chronic abscess.

If improvement is not manifest after a reasonable period of medical treatment, that is, if adequate drainage has not been established, surgical intervention is indicated. It then becomes a question as to the particular procedure best suited to the case. Graham says, in regard to this, that we must first determine: (1) Whether the abscess is single and well encapsulated; (2) whether the area of pulmonary involvement is diffuse, with multiple abscesses occupying a considerable portion of a lobe; (3) whether it is chiefly a bronchiectatic dilatation; (4) whether it is central or peripheral; and (5) whether pleural adhesions are present. Incision and drainage is probably the operation indicated in all peripheral abscesses which do not show definite improvement on expectant treatment, and is better performed under local anaesthesia, because of the danger of the aspiration of pus into the other lung or good portions of the affected lung. In order to ensure adequate drainage over a considerable period of time, such as is indicated in these cases, it is necessary to do a rib-resection, possibly of more than one rib. If pleural adhesions are present (this can be determined prior to the operation by the use of the manometric attachment of the artificial-pneumothorax apparatus), locate the abscess with a needle, and then go through the lung tissue with a blunt instrument or with the actual cautery. Insert a soft rubber-tube drain, and assist drainage by posture. If adhesions are not present, the operation should be done in two stages, packing with gauze after the first stage to promote adhesions. The complication of gangrene adds materially to the surgical risk. Hartwell and Dudley state that following such an operation, and in uncomplicated cases, healing is expected with obliteration of the cavity in about two months. If the abscess has a large opening into a rigid bronchus there is a possibility of bronchial fistula, which may persist for a long time, or permanently. Secondary hemorrhage is a serious postoperative complication with high mortality.

Extrapleural thoracoplasty is indicated in the same type of case as artificial pneumothorax would be, were there no pleural adhesions present. It is used in the chronic cases with multiple bronchiectasis. It

consists in the resection, in stages, of the whole length of all the ribs over the diseased area. Hedblom has performed 18 such operations with good results and no mortality. He says, "There are many bad results, probably due to failure to perform an extensive enough operation, or to too extensive an operation at one sitting."

Lobectomy is indicated, according to Hedblom, in those cases in which the abscess is multilocular from the onset, in others in which secondary abscesses develop after drainage of the primary one, and in the more chronic cases with extensive associated pneumonitis, fibrous thickening of both lungs and pleura, and bronchiectasis, making either collapse or drainage treatment ineffective. Hedblom advises the cautery method as the safest and most effective, provided late hemorrhage does not prove too frequent and fatal a complication. Graham states that by original methods of doing this operation the mortality was 50 per cent. Graham advocated, in 1923, a partial pneumonectomy with the actual cautery, waiting preferably until the acute stage was past. His technique is as follows: The patient empties his lungs by inverted position just before operation. Adhesions to the chest- wall are necessary, and if not present must be induced. After the indicated incision through the chest-wall the diseased area is attacked with a red hot soldering iron, making an excavation in the lung tissue. The operation is done in as many stages as seem indicated, a large cavity with a charred wall remaining at its completion. Secondary haemorrhage is theoretically to be feared, but has not occurred in his cases. He thinks that, if it did, it should be easily controlled with packing, because of the low pressure in the pulmonary artery. He has reported 17 cases with one death. He recommends, in the after-treatment, heliotherapy and exposure of the wound to the air.

Artificial pneumothorax is indicated only in centrally located abscesses, when there are no pleural adhesions and the abscesses are favorably situated for drainage through a bronchus. These deep-seated abscesses are difficult and dangerous to operate upon because of the danger of hemorrhage. Only a small percentage of cases are suitable for this procedure, which is contraindicated in the peripheral abscesses because of the adhesions which prevent collapse, or, by pulling upon the abscess wall, cause tearing, with rupture of the abscess into the pleural cavity, and resulting empyema, a most serious and frequently fatal complication. With multiple abscess, pneumothorax is unsatisfactory. Tewksbury reports 14 cases of artificial pneumothorax with 11 cures and 2 deaths. Ferguson had 6 cases with satisfactory results in one only. All of these, however, were very chronic cases.

Graham thinks the bronchoscope valuable for the removal of foreign bodies, the drainage of centrally located abscesses, or to determine whether pus is coming from the middle or lower lobe. He quotes Chevalier Jackson as saying that "in no case of lung abscess should bronchoscopy be used for treatment and thoracotomy delayed." Hartwell and Dudley quote Hoover, who considers severe pulmonary hemorrhage the only contraindication to bronchoscopy in pulmonary abscess. He thinks the bronchoscope should be used before major surgery. The abscess cavity does not need to be entered directly, the pus being withdrawn from the bronchus into which the abscess empties, this serving to drain also the contiguous area. Hoover advises starting the treatment as soon as purulent expectoration is noted, and repeats it weekly until the patient is cured. Improvement is less satisfactory in the chronic cases. It is not believed that this method of treatment will receive widespread favorable recognition, as it requires a skilled specialist who is not generally available to the ordinary clinic, where any of the other methods of treatment mentioned above could be satisfactorily carried out.

Another method of treatment has been tried out by Ferguson, who claims good results in some cases. He tried exploratory pulmonary puncture, aspirated the cavity, and injected bismuth paste. He thinks that it has curative value in chronic cases in which the bismuth is retained, but notes that the method is not without danger of serious complications. It is not probable that this adds anything of value to the treatment of pulmonary abscess. Hoover, however, thought well of a somewhat similar procedure. In old cases, in which drainage was not successful by means of the bronchoscope, he injected through the bronchoscope a bismuth mixture in pure olive oil, following this with X-ray exposure. Two or three of the treatments can be used, and Hoover reported three out of five cases as cured, having no symptoms for one year.

Whatever the method of treatment, medical or surgical, it is necessary to plan for the patient's proper care during a certain period of convalescence, before resumption of occupation is possible. Klapper has had considerable experience during the past seven years in the convalescent care of this class of cases, his methods being much the same as those in vogue for convalescent tuberculous cases. He quotes Lockwood as recommending long after-care, one to two years, in a dry sunny climate, but the patient should not go too far from the zone in which he intends to make his livelihood. While a gradual return to the patient's normal

activities is indicated, with the supervision of a physician during this period, it is not believed by the writer that such a long period or too elaborate a regimen is indicated, certainly not in cases that may be considered as cured, that is, healed. If they do not belong in this class, then further treatment along the indicated lines should be carried out. It is appreciated that certain of the etiological factors, or the occurrence of some of the serious complications, would indicate a more prolonged and more carefully guarded convalescence.

Several of the cases admitted to this hospital (Fort Sam Houston) within the past two and one-half years have possessed considerable interest as illustrating certain points mentioned in the brief presentation above. Further, it is possible to demonstrate, by serial X-ray plates, the progress under treatment in these cases. For the purpose of differential diagnosis there is also presented a case of bronchiectasis and one of encapsulated, interlobar pleurisy with effusion.

Of the 17 cases of lung abscess in this series, 15 were cases of single abscess and 2 cases of multiple abscess. The etiology in one case was extension from an amoebic liver abscess, in six lobar pneumonia, in one the abscess followed tonsillectomy, in one bronchopneumonia. In eight the etiology was undetermined. The infecting microörganisms were the streptococcus in three cases, the pneumococcus in four, mixed streptococcus and staphylococcus in three and unknown in seven cases.

Eleven of the cases were acute, including both of the multiple-abscess cases, and six chronic. Of the 15 single abscesses, 10, or 66.6 per cent, were in the right lung, and 10, or 66.6 per cent, in the lower lobes, or, if the right middle lobe should be considered as a lower lobe, 11, or 73.2 per cent, were in the lower lobes. Five cases were in the right lower, 5 in the left lower, one in the right middle and 4 in the right upper.

In the 17 cases there were 7 cured, 2 improved, one unchanged, 2 remaining in the hospital, and 5 deaths, a mortality rate of 33.3 per cent. Of the 2 cases remaining in the hospital one is a child four years of age, who was brought to the hospital with an empyema in the right side, following what had been diagnosed as a lobar pneumonia. After drainage of the empyema it was discovered that there was some involvement of the right upper lobe, and definite symptoms of a lung abscess appeared about ten days later. This patient has practically recovered on postural drainage and will be ready to go home in a short time.

The second case was admitted to the hospital with a left hemiplegia, flaccid in type, and a history of headaches and vomiting. The patient

had a chronic lung abscess in the right lower lobe of ten or eleven months' duration, having been operated upon for it in March, 1925. A diagnosis of brain abscess, secondary to lung abscess, was made, and he was operated upon. The abscess was located and drained, but his recovery is doubtful. No definite treatment has been directed toward the lung abscess.

The mortality among the cases coming into the hospital as single abscess cases and in which hospitalization has been completed, was 3 out of 13, or 23 per cent. All of these died of complications, one of suppurative pericarditis and nephritis living only three days after admission. Deducting this case as hardly chargeable to the hospital, the rate would be 15.4 per cent. The other two died of pyothorax and secondary multiple abscesess.

The mortality among cases coming into the hospital as multiple abscess cases was 100 per cent (two cases).

Incision and drainage, 3 cases, gave a mortality of 66.6 per cent, only one being cured. In both fatal cases, however, the operation was performed on complications arising, one from medical and one from pneumothorax treatment, and can hardly be charged to the surgery. One case was cured by incision and drainage.

Of the three artificial-pneumothorax cases, two were improved and one died following pyothorax, incision and drainage, and later multiple abscesses, a mortality of $33\frac{1}{3}$ per cent for pneumothorax.

The complications noted were purulent pericarditis, one case; spontaneous pneumothorax, two cases, one following artificial pneumothorax; empyema with bronchopulmonary fistula, one case; and brain abscess, one case.

Six of the cases are reported, one or more of the serial X-rays being presented in each case as illustrative of certain pathological types or showing the changes taking place under treatment.

Case Reports

Case 1: M. E. M., register no. 121,180, white, male, 22 years of age, admitted October 28, 1923. *Family history* unimportant. *Previous personal history* negative, as far as antecedent factor for lung abscess was concerned. Never had any diseases of the respiratory tract. No sinus trouble, dental work, operations on nose or throat, only being under anaesthetic once, in 1918, for amputation of second and third toes, left foot. Discharged from Service on Surgeon's Certificate of Disability, September 5, 1922, on account of diabetes mellitus, the latter being the cause of admission to this hospital. *Symptoms*

on admission: Weakness, thirst, polyuria, polydipsia, loss of weight. *Physical examination on admission:* Underweight; nothing else of importance noted. X-ray of lungs showed cavity in right lower lobe, toward base, about 5 cm. in diameter, with fairly thick fibrous wall. No inflammatory reaction in surrounding lung tissue. Eyes negative. Dental examination showed gingivitis. Urine showed sugar and acetone. The sputum, which was very scanty, was repeatedly negative for tubercle bacilli. Blood picture normal. Blood Wassermann negative. Blood chemistry showed blood sugar 0.30 per cent, uric acid 5.51, otherwise negative.

Patient was placed on insulin treatment for diabetes mellitus, and, when he coöperated, did very well. He was very uncoöperative, however, and at times would refuse to take his insulin, and did not adhere to his diet. Nevertheless, he improved, gained 15 pounds in weight, felt much stronger, and the polyuria and polydipsia disappeared to a considerable extent. There were practically no cough or expectoration, or symptoms of any kind from the lung cavity, and no treatment was directed to it.

On November 29, 1923, he was given a two-hour pass to visit his home in San Antonio, Texas. While at home he developed a spontaneous pneumothorax on the right side, from rupture of the cavity. He denied undergoing any exertion or effort. As the patient was getting 15 units of insulin, t.i.d., at the time, his weakness, dyspnea, collapse and rapid pulse suggested at first an insulin shock, that is, hypoglycemia, but urine and blood examinations ruled this out and thorough physical examination then revealed the pneumothorax. In a few days he developed fluid in the pneumothorax cavity. Following this he refused to take his insulin, and his case became retrogressive. The temperature, hitherto always normal, became slightly elevated, and the pulse rapid, 80 to 120. Later he permitted some insulin treatment, and his downward course was partially checked. He left the hospital January 22, 1924, against medical advice, and it was reported later that he had discontinued all treatment and died.

Note: Single, chronic abscess of right lower lobe, in diabetic patient, etiology unknown. Gave no symptoms. Later ruptured with resulting hydropneumothorax. No treatment had been directed to abscess, none being indicated. (See figure 1.)

Case 2: R. C., register no. 130,640, age 38 years, white, male, admitted February 18, 1925, occupation blacksmith. *Family history* unimportant. *Previous personal history:* Influenza and pneumonia in 1919. No injuries or operations. Claims to have had cough since discharge from Service in 1919, and has been treated off and on by various doctors and in various hospitals since discharge. Has always been under the impression that he had pulmonary tuberculosis, but this condition has not been found to be present at the hospi-

tals where he has received treatment. *Symptoms on admission:* Cough, 60 to 80 cc. of mucopurulent sputum daily, pain in both sides of chest, upper right and lower left, sometimes over entire left side, 20 pounds underweight. *Physical examination* was negative, except for clubbing of fingers and toes and pulmonary findings (deficient expansion, impairment of percussion note, increased vocal resonance, bronchovesicular breathing and whispered pectoriloquy, over left lower lobe). Cough paroxysmal and brought on by change in posture. Expectoration fetid, slightly blood-tinged at times. Temperature on admission showed occasional elevations to 99.2°, pulse 80 to 112, respiration 20. Ears, nose and throat negative. Dental examination showed slight pyorrhea. Eyes negative. X-ray of chest showed an opacity in the left lower lung, about size of baseball, rather sharply circumscribed and resembling an area of unresolved pneumonia. Urine negative, stools negative, sputum negative for tubercle bacilli, red blood cells 4,220,000, hemoglobin 80 per cent, leucocytes 9,400, polymorphonuclears 68 per cent, Wassermann negative.

Treatment: Postural drainage was first used, with no special benefit, except some relief of cough. Various medicinal remedies were also used for relief of cough, as well as steam inhalations, the benefit from the latter being only relief of the irritation in the upper respiratory tract. Artificial pneumothorax was started April 24, 1925. Following this treatment the cough decreased, but, as the lung was gradually compressed, expectoration was very considerably increased from 120 to 360 cc. in twenty-four hours. The character of the sputum gradually changed from purulent and fetid to mucopurulent, nonoffensive

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FIG. 1. CASE 1. SINGLE, CHRONIC ABSCESS, RIGHT LOWER LOBE, IN DIABETIC PATIENT, CAUSE UNKNOWN

Gave no symptoms. Later ruptured with resultant hydropneumothorax. No treatment had been directed to abscess, none being indicated.

FIG. 2. CASE 2. SINGLE, CHRONIC ABSCESS, IN LEFT LOWER LOBE, CAUSE UNKNOWN

Treatment: Medical and artificial pneumothorax. Result improved. Condition at beginning of treatment.

FIG. 3. CASE 2. FIGURE HAS BEEN RETOUCHED TO BRING OUT LIMIT OF COLLAPSE BY ARTIFICIAL PNEUMOTHORAX

After partial collapse of lung by artificial pneumothorax. Pleural adhesions due to a previous artificial pneumothorax prevented further collapse with the neutral or very low positive pressure used.

FIG. 4. CASE 2. FIGURE RETOUCHED TO BRING OUT DETAIL OF PNEUMOTHORAX

At completion of treatment. A very thin layer of air left at the anterior base. Patient showed no symptoms and few physical signs.

FIG. 5. CASE 3. SINGLE ABSCESS, ACUTE, RIGHT UPPER LOBE, SECONDARY TO BILATERAL TONSILLECTOMY DONE UNDER GENERAL ANAESTHESIA

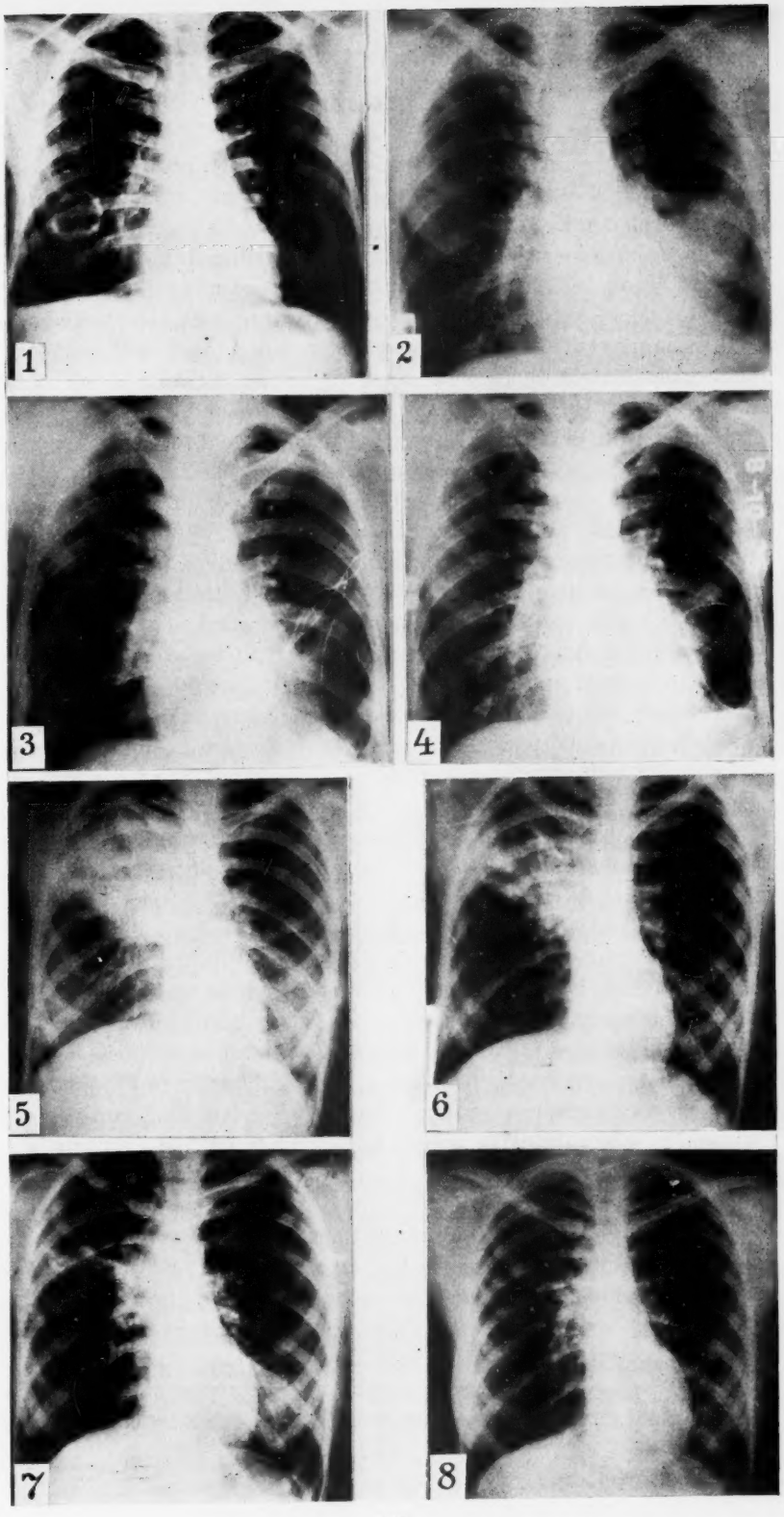
Mixed infection (staphylococcus and streptococcus). At beginning of treatment.

FIG. 6. CASE 3. AFTER FIVE DAYS ON POSTURAL DRAINAGE

FIG. 7. CASE 3. CONTINUED CLEARING ON POSTURAL DRAINAGE

Plate taken fifteen days after beginning of treatment

FIG. 8. CASE 3. FINAL RESULT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type. Patient's general condition remained good, with occasional elevations of temperature to 99.6° in the first part of the treatment, pulse and respiration remaining unchanged. It was only possible to obtain a partial collapse of the lung, due to adhesions. (Patient had had an artificial pneumothorax previously, in November, 1923.) The collapse obtained was sufficient, however, to cause considerable compression of the suppurating area and marked symptomatic improvement. The cough and expectoration practically disappeared. Patient gained weight and was feeling much better. Because of the contraction of adhesions the air-space was gradually lost, and pneumothorax was discontinued July 19, 1925. During the pneumothorax treatment postural drainage and heliotherapy had been continued. (General radiation.) At the conclusion of the pneumothorax treatment, the temperature was normal and had been practically so for two months. Pulse still a little rapid, respiration normal. As symptoms had disappeared, physical findings improved, and the X-ray showed the area involved to have practically cleared up, it was considered that maximum hospital benefit had been obtained, and the patient was discharged August 13, 1925, being told that, if the condition returned, operative procedures, in the nature of thoracoplasty, would be indicated.

Note: Single, chronic abscess, in left lower lobe, cause unknown. *Treatment:* Medical, and artificial pneumothorax. *Result: Improved.* (See figures 2, 3 and 4.)

Case 3: A. K., register no. 127,421, civilian, female, age 19 years, white, admitted September 24, 1924. *Family history* unimportant. *Previous personal history* unimportant, except for tonsillectomy June 28, 1924, under general anaesthetic. *Onset of present disease:* Had had attacks of tonsillitis, beginning at 5 years. Peritonsillar abscess at 14 years. Tonsillectomy June 28, 1924, under general anesthetic. Five days after operation she took a three hundred mile automobile trip. Had apparently made an excellent convalescence from the operation, but about two weeks later had sensation of chilliness and fever. A few days later developed a persistent cough, with rather profuse expectoration, which soon became offensive in nature. She has since had periods of improvement, when the expectoration and cough would cease and she would feel well. One week ago, after such a period of freedom from symptoms, had another onset of fever, the cough returned, and the expectoration became profuse. This has persisted until present time. *Condition on admission:* Temperature 101.2°, pulse 120. Has cough, especially in the mornings following breakfast, and gets up a considerable amount of sputum at this time. Has a constant dull pain in the right side of the chest, anteriorly, in the right pectoral region, and posteriorly under the right shoulder blade. Pain is sharp when coughing. Sleep is interrupted by coughing. The expectoration is profuse. Has lost weight and has more or less fever. *Examination on admission:* Has

constant cough. Looks anemic and has lost some weight. Blood pressure 116/72. Over right upper lobe of the lung there is a slight typanitic percussion note and prolonged expiration; no râles are noted. Physical examination otherwise negative. *X-ray of right chest:* 1st and 2nd interspaces show an area of infiltration, with a central irregular clearer area. The periphery shows gradual diminution of the density. Urine showed albumen double plus, few pus cells, many blood cells. Stool negative. Sputum negative for tubercle bacilli. Culture of sputum showed a mixed infection, with no type predominating. The smear showed many pus cells and many bacteria of mixed types. Red blood cells 3,550,000, hemoglobin 75 per cent, leucocytes 19,200, polymorphonuclears 84 per cent, blood culture negative, Wassermann negative.

Treatment: Postural treatment, 5 minutes t.i.d. Syrup of iodide of iron. The expectoration was at first about 400 cc. daily, and offensive in odor and taste. Cough excessive. Temperature of septic type, and ranging from 99.6° to 102.3°; pulse 98 to 130, respiration 20 to 26. Under postural drainage (5 minutes t.i.d.) patient improved rapidly. Temperature and pulse came to normal in two days, the cough and expectoration were markedly diminished, the appetite improved, and the patient slept much better. The improvement was rapid and continuous, as evidenced by the clinical course, physical findings and X-ray. The patient was discharged from the hospital on October 15, 1924, after three weeks' treatment, in excellent general condition, with no cough or expectoration, temperature normal, and with a gain in weight. She was seen again about three months after leaving the hospital and remained perfectly well at that time.

Note: Single abscess, acute, right upper lobe, secondary to tonsillectomy, bilateral, under general anesthesia, performed at civilian hospital, June, 1924. Mixed type of infection. Cured by medical treatment. (See figures 5, 6, 7 and 8.)

Case 4: C. D. W., register no. 129,195, male, white, 38 years, admitted to hospital January 1, 1925, occupation, farmer. Had two years' service in the Philippine Islands. Has not used alcohol since 1921. Drank whiskey to excess prior to that date. *Family history* unimportant. *Previous personal history:* Remembers no diseases of childhood, except "ground itch." Had a shrapnel wound of left cheek, in action, in France, 1918, and a liver-abscess drainage in October, 1924. Had gonorrhoea in 1911. While picking cotton, November, 1924, he had a sharp, intermittent pain in the right side, over the ribs, this kept increasing in severity, and shifted its location to one inch below the right nipple. Patient was taken to a hospital on October 3, 1924. Abscess of liver was drained on October 7, 1924. Recovery was uneventful, and all symptoms disappeared. Patient states that he has been gradually gaining strength since his operation and slightly in weight. Appetite and digestion have been good,

but for the last three weeks has had a cough, worse at night, and has been expectorating considerable blood and pus. For three days before admission to this hospital (Fort Sam Houston) he has had pain in his right side, similar to that present before his operation, except that the pain is more continuous in character and worse during the night. *Condition on admission:* Looks chronically ill, anemic and underweight; has a cough and considerable pain in the liver region. Temperature 101.2°; pulse 120; respiration 28. *Physical examination:* Normal weight 135 pounds dressed; present weight 96 pounds stripped. General condition weak, anemic and emaciated. Skin and mucous membranes anemic and pale, with slight injection of the pharynx. No adenopathies. No sclerosis or varicosities of vessels. Blood pressure 100/65. Heart not enlarged, regular, no murmurs, sounds normal. *Lungs:* Decreased resonance, feeble breath-sounds and few large moist râles, right base, posteriorly. Genitourinary system, no scars or discharge. Abdomen scaphoid, scar of right rectus incision, liver 1 cm. below costal margin, spleen not palpable. Tenderness marked over 5th rib to costal margin, right. No masses. Nervous and osseous systems negative. Muscles show marked wasting. Joints negative. Dental examination showed dental caries and pyorrhoea, slight. Eye, ear, nose and throat examinations negative. Leucocytes 14,800, with 79 per cent polymorphonuclears. Urine negative. Patient had severe, intermittent cough, bringing up a frothy hemorrhagic sputum. With a history of an old liver abscess the symptoms suggest perforation through the diaphragm into the right lung. Patient's general condition was poor. He coughed up about 100 cc. of bloody sputum between 7 P.M. and midnight, January 2, 1925. Consultation with the surgical service on January 3 led to recommendation of transfer to surgical side for further observation. Patient was transferred on January 3 to surgical side. The first Wassermann was plus-minus. Blood count on January 5 showed 3,400,000 reds, 65 per cent hemoglobin and 14,200 whites, with 75 per cent polymorphonuclears. Three sputums were negative for tubercle bacilli. Another urine was negative, except for a few hyaline casts. An X-ray of the chest showed some scattered densities in the apex, 1st, 2nd and 3rd interspaces, right, with indications of a cavity, opposite 8th to 10th ribs, posteriorly. The cavity showed a fluid level with area of infiltration extending down to the diaphragm. The left chest was negative.

Patient was operated on for suspected liver abscess January 8, 1925, with resection of 8th rib, right, with exploration of liver, but no pus was found. Following the operation he had acute pain in the right side, with expectoration of blood. The stitches were removed on January 13, and he was returned to the medical service.

He continued to suffer from considerable pain in the right lower lung field. Sputum bloody. Another blood count showed 3,700,000 reds, 75 per cent hemoglobin, 15,300 whites and 73 per cent polymorphonuclears. Urine at this

time showed double-plus albumen and many hyaline and granular casts. Patient had an irregular septic temperature, averaging between 97° and 100° plus daily: pulse about in proportion to temperature. He was placed upon postural drainage, night and morning, and treated expectantly. He showed some improvement, but symptoms were much the same.

On January 21, he coughed up about 260 cc. of bloody, purulent sputum in the 24 hours, and continued expectorating about this amount. Temperature averaged from 98° to 101°; pulse 88 to 128. Another X-ray of chest, January 27, showed a diffuse density in the right chest, extending from 7th rib posteriorly to the diaphragm. Patient continued to have pain over the liver region and to be quite tender to pressure in this area, and his leucocyte count was then about 18,000, with 70 per cent polymorphonuclears. X-ray of the sinuses was negative. Patient gained a few pounds in weight, but began losing again, all symptoms being increased in severity; his temperature range became higher and remained around 101°, occasionally going as high as 102° plus. Appetite poor. Pulse rapid, 100 to 120. Leucocyte count decreased somewhat. Examination of sputum for amoebae was negative, but stools showed many *Amoeba histolytica* present. Urine showed trace of albumen and many hyaline casts. In view of the continuation of symptoms patient was returned to the surgical service for further operative procedures, and was operated upon again on February 13, 1925, with excision of about two inches of the 9th rib and evacuation of pus. His improvement after this operation was rapid and uneventful. At the expiration of one week his temperature had returned to normal, and remained so until time of discharge from hospital. Smear and culture of pus obtained contained no amoebae, no microörganisms, and the culture was negative. Wassermann negative. Two examinations of stools in March were negative for amoebae. Urine negative. An X-ray of chest on March 8 showed the right diaphragm elevated with some fibrosis in the right lower lobe, but no evidence of cavity. Patient had been given a course of emetin hypodermatically and ipecac by mouth. Patient was discharged in good physical condition on April 21, 1925.

Note: Single, acute abscess, in right lower lobe, due to extension of amoebic liver abscess through diaphragm, no secondary microörganisms being found. Treatment by incision and drainage. Cured. (See figures 9, 10 and 11.)

Case 5: A. T., register no. 130,030, male, white, 21 years, admitted January 26, 1925. *Family history* unimportant. *Previous personal history:* No previous serious illness. *History of present disease:* For the past two weeks has had cough with pain in right side, in anterior axillary line. Cough has grown worse and has had headaches for the past two or three days. *Condition on admission:* Severe, dry cough, with pain in right side of chest; temperature 99.6°; pulse 110; respiration 22. *Examination on admission:* General condition appears good.

Is well-nourished. Special senses normal. Skin and mucous membranes negative, except for redness and inflammation of pharynx. No palpable lymph nodes. Vascular system negative. Heart negative. *Lungs:* Hyperresonant percussion note on right side, with increased fremitus and a few scattered musical râles anteriorly. Physical examination otherwise negative. Urine negative, two examinations. Stool negative, one examination. Sputum negative for tubercle bacilli, four examinations. Culture for prevailing microorganisms showed pneumococcus. Leucocytes 8,850, reds 4,260,000, hemoglobin 80 per cent, polymorphonuclears 66 per cent. Wassermann negative.

Progress: After two days in the hospital the throat condition cleared up, and patient's temperature and pulse dropped to normal. The cough, however, continued. On January 30, four days after admission, the cough had improved somewhat, but patient began running an evening elevation of temperature and said that he perspired profusely at night. He lost some weight, showed decreased resonance to percussion on right side of the chest, with increased vocal fremitus and bronchovesicular breathing, but râles were absent. On February 6, a summary of his case showed him complaining of slight cough and expectoration of one month's duration, and no pain in chest. Symptoms improving. Loss of about 10 pounds in weight. Physical examination showed decreased resonance on the right side, clavicle to 2nd rib, and with bronchovesicular breathing in the right infraclavicular fossae. Tactile fremitus increased right upper lobe. Slight drooping of right shoulder. Indefinite râles heard above 2nd rib on right, at the end of inspiration, which did not disappear after cough; on this date an X-ray showed, right lung, apex clear, and a dense globular mass the size of a baseball occupying the middle third of the lung in

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FIG. 9. CASE 4. SINGLE, ACUTE ABSCESS, IN RIGHT LOWER LOBE, DUE TO EXTENSION OF AMOEBIC LIVER ABSCESS THROUGH DIAPHRAGM, NO SECONDARY MICROORGANISMS BEING FOUND

Cured by incision and drainage. Appearance at time of admission.

FIG. 10. CASE 4. APPEARANCE PRIOR TO SECOND OPERATION, INCISION AND DRAINAGE

FIG. 11. CASE 4. AT COMPLETION OF TREATMENT

Incision healed

FIG. 12. CASE 5. PLEURISY, SERO-FIBRINOUS, INTERLOBAR, ENCAPSULATED BETWEEN UPPER AND MIDDLE LOBES, RIGHT LUNG

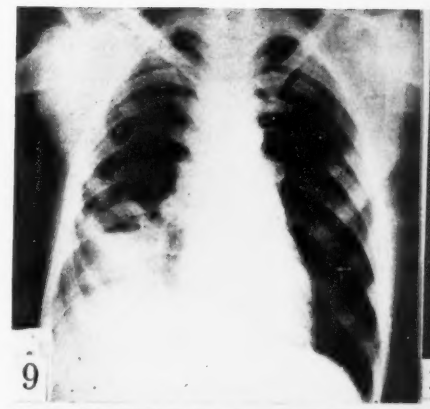
Sharply delimited outline, no evidence of cavity. Cough was practically unproductive. The location of the mass is also very suggestive.

FIG. 13. CASE 5. APPEARANCE AFTER ABSORPTION OF FLUID

Note interlobar pleural thickening

FIG. 14. CASE 6. MULTIPLE BRONCHIECTASIS, CHRONIC, LEFT LOWER LOBE, FOLLOWING LOBAR PNEUMONIA (PATIENT'S STATEMENT)

Blastomycotic secondary infection. No improvement under medical treatment. Operative procedures refused. The reduction unfortunately does not bring out the details of the pathological changes. The lower third of the left lower lobe is filled with dilated bronchi, the appearance being similar to that of a large honeycomb.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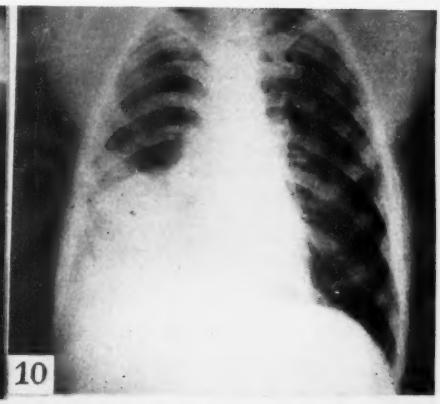
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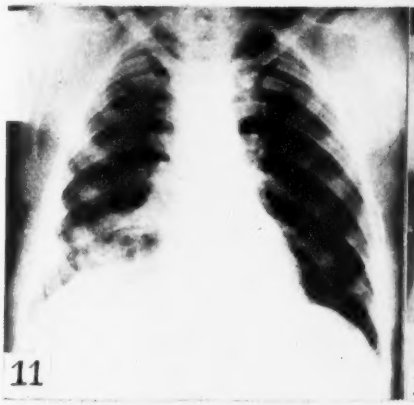
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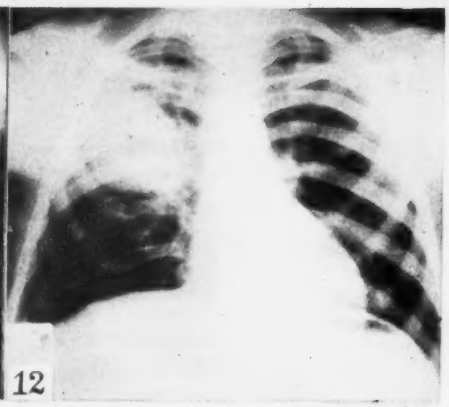
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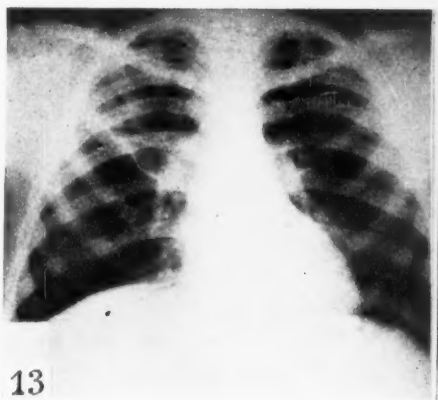
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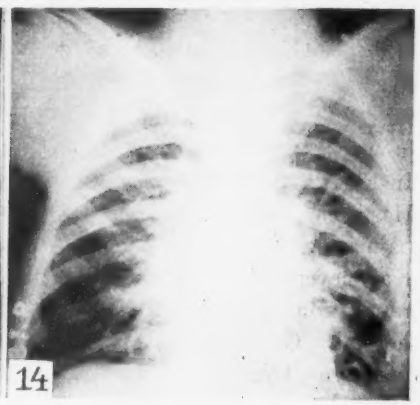
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the 1st, 2nd and 3rd interspaces. The base and costophrenic angle clear. The temperature at this time had been normal for two days. Patient showed continuous improvement, was looking and feeling well, appetite good, temperature and pulse remaining normal, and regaining steadily in weight. Cough slight, expectoration scanty. By March 2 the physical findings had cleared up, and an X-ray plate showed the globular mass in the right lung to have disappeared. In its place was a linear shadow, suggestive of interlobar pleural thickening. This supported the view that the shadow previously reported was a circumscribed collection of fluid between the interlobar septa. Patient was discharged March 15, 1925, with diagnosis of pleurisy, sero-fibrinous, interlobar, encapsulated between upper and middle lobes, right lung.

Note: Had gradual onset, cough, pain in chest. Physical findings indistinguishable from abscess, little expectoration, not purulent, temperature not of septic type and became normal after eleven days. Patient clinically did not appear septic. The treatment was that usually directed toward promotion of absorption of a pleural (or other) effusion. (See figures 12 and 13.)

Case 6: I. C. C., register no. 134,077, male, 29 years, colored, admitted to hospital July 15, 1925, left absent without leave July 25, 1925, and readmitted August 19, 1925. *Family history* unimportant. *Previous personal history:* Had pneumonia in left lower lobe, in France, in 1918. Mumps in 1918. Gunshot wound junction middle and upper thirds, right thigh, 1922. Gunshot wound left upper chest, penetrating, entrance outer border pectoralis major, level 3rd interspace, exit just below point of scapula, 32-calibre pistol, 1923. *History of present disease:* Discharged from Service April 29, 1919, on Surgeon's Certificate of Disability, on account of unresolved pneumonia; about fifteen days following the pneumonia in the left lower lobe, in 1918, patient began to have a large amount of foul-smelling sputum. This has continued until at time of admission to this hospital (Fort Sam Houston). He stated that he raised about one-half pint of sputum each morning. Following his discharge he went back to work, but at his first medical examination lost his position. In 1923 was at Camp Logan, and left against medical advice, after six days. Has been in no other hospital. *Condition on admission:* Complained of cough, pain in left lower chest, about one-half pint of foul smelling sputum daily. Has never had a pulmonary hemorrhage. Temperature 97.6°, pulse 90, respiration 18. *Physical examination on admission:* Ambulant. Weight about normal. General condition appears good. Skin and mucous membranes negative. Lymph nodes, no adenopathy noted. Vascular system, varicocele, slight, left, no other varicosities, no sclerosis. Blood pressure 122/80. Heart shows systolic murmur over base. Heart seems a little enlarged to right. Lungs show exaggerated breathing over right side. There is diminished expansion at the left base. Decreased resonance left, from 3rd rib and 6th dorsal spine to

base. Complemental space absent on left. Increased fremitus 3rd rib and 6th dorsal spine to base, left. The breath-sounds are cavernous; there is whispered pectoriloquy and gurgling râles over left base, posteriorly and laterally. Genitourinary system, including prostate, negative. Abdomen, normal contour; liver not enlarged; spleen not palpable; no tenderness or masses. Nervous system, pupils equal, slightly irregular, react promptly to light and accommodation, no Romberg or Babinski, tendon reflexes present. Osseous system, muscles and joints negative. Ears, nose and throat negative. Larynx negative. Dental examination showed caries R 15, 7 and 6. Eye examination negative. X-ray showed the lower third of left lung filled with fibrous tissue. Lung in the form of a very large honeycomb. *Impression:* Multiple cavitation in left lower lobe, cause undetermined. Urine showed trace of albumen and many pus cells on first examination, two successive examinations being negative. Stools negative. Sputum negative for tubercle bacilli on five examinations. The culture of sputum for fungi was positive on three successive occasions for Blastomycetes. Blood examination showed 4,000,000 reds, 14,600 whites, and 69 per cent polymorphonuclears. Malaria negative, two examinations. Two blood Wassermanns negative.

Progress: Patient went away without leave on July 24, 1925. He had been put on postural drainage shortly after admission, and was raising about 250 cc. of foul, purulent material daily. Temperature had been normal, and general condition good. Diagnosis at this time was bronchiectasis, multiple, left lower lobe. On return to hospital on August 19, 1925, general condition and chest findings were unchanged, except that the systolic murmur previously heard over the precordium had disappeared. Following his readmission patient got along only fairly well. Postural drainage was continued, large quantities of foul sputum being raised. If patient missed a drainage period he would have occasional paroxysms of coughing, at which time considerable quantities of this material would gush from his nose and mouth. He was also placed on graduated doses of potassium iodide, beginning with ten drops and increasing, this because of the blastomycetes, secondary infection. His complaints were, in addition to the expectoration, some pain in the chest and in the cardiac region, with occasional shortness of breath. The systolic murmur over the precordium was absent at times and present at other times. A rough systolic murmur over the aortic area was constantly present. He left the hospital against medical advice on September 26, 1925. His weight at time of departure was 178 pounds, a gain of 3 pounds. Temperature had been normal at all times. Pulse 76 to 112; respiration 18 to 24. He was still having moderate cough and still raising about 250 cc. of a fairly thin purulent, offensive sputum. Advised that operation would be necessary if any benefit was to be obtained.

Note: Multiple bronchiectasis, chronic (seven years' duration), in left lower

lobe, following lobar pneumonia. Blastomycotic secondary infection. *Treatment:* Medical; no improvement. Indications in this case are for operative procedures, probably lobectomy, or, less promising, thoracoplasty.

Note the absence of septic manifestations, the very abundant, thin, foul sputum, the tendency to gushing forth of large amounts of sputum following a moderate paroxysm of coughing, brought on by movement and changes of position. Also the very moderate leucocytosis and the appearance of the X-ray picture, showing many dilated bronchi, these in contradistinction to lung abscess. (See figure 14.)

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COMBINED ARTIFICIAL PNEUMOTHORAX AND THORACOPLASTY

With Report of a Case[1]

CLOUGH TURRILL BURNETT

In his new book on *The Surgery of Pulmonary Tuberculosis* Alexander discusses at some length the combined use of induced pneumothorax and thoracoplasty, a procedure first proposed by Brauer in 1909 and later advised independently by Wilms and Sauerbruch in 1913. As advantages of this method over complete thoracoplasty Alexander mentions: *1:* The operative risk is less because the circulatory and respiratory organs are accustomed to the change that will occur with thoracoplasty, partial or complete. *2:* The danger of aspiration of infected secretions is lessened by virtue of the diminished or absent respiratory movements in the lower lobes. *3:* The thickened pleura, resulting from the continued induced pneumothorax tends to fix the mediastinum against undue displacement resulting from the operation. *4:* The more diseased lobe is permanently compressed for the length of time desired, allowing for a possible reëxpansion and resumption of function later. This is also especially desirable in case of reactivation or extension in the contralateral lung. *5:* One entire operative stage is avoided, unless later events prove the necessity of permanent compression of the lower lobe.

Eloesser, Riviere, Hauke and, until recently, Sauerbruch considered this an ideal procedure. Practically all of the objections raised to this technique have been recorded during the past two years. In the latest edition of his *Chirurgie der Brustorgane* (Vol. I, p. 731) Sauerbruch states, "The numerous favorable results, which I have seen, lead me to consider the combination of the two methods (pneumothorax and thoracoplasty) to be the ideal surgical treatment of unilateral pulmonary tuberculosis.

Brunner, apparently writing for the Sauerbruch Clinic in 1924, stated that extrapleural thoracoplasty combined with an existing pneumothorax is technically a very difficult operation, since the costal pleura outside of the adhesion is very easily broken. In a final summary of their cases he states that the results are not striking. He emphasizes the probability of ultimate obliteration of the space and the danger of mixed infection,

[1] Read before the Denver Sanatorium Association, Denver, Colorado, November 24, 1925.

and further cites two cases in which after long continued pneumothorax the lung would not reëxpand.

Davies, in 1923, raised somewhat similar objections. He doubted whether it would be possible to maintain the pneumothorax long enough, because eventually the final stage of the thoracoplasty would probably be less successful (on account of regeneration of bone) than if it had been performed in direct connection with the first-stage operation. It would seem to the writer, however, that the advantage of avoiding a stage of a major operation would be sufficient to outweigh this objection. Jensen, Ziegler, Gravesen, and Brauer and Spengler prefer the complete operation in severe and extensive cases. Alexander considers the presence of an effusion in the pneumothorax cavity a definite indication for the complete operation, for the reason that "the 'pneumothorax lobe' would probably be pulled out too soon by pleural adhesions." Most of us have had numerous experiences with the complicating effusion of induced pneumothorax, some with the final obliteration of the space, but also not an inconsiderable number in which the effusion was absorbed without any effect whatsoever; and even in the cases which progressed to obliteration this did not occur for many months, which often would be sufficient for arrest of the progressive disease in that portion of the lung. Alexander's rule, that "partial thoracoplasty should never be undertaken as a final operation unless the artificial pneumothorax is at least 50 per cent complete," is undoubtedly sound, for extensive basal adhesions would probably never permit functional rest of the lower lobes. The only exception to this would be those extremely rare cases in which the disease, in the portion of the lung to be maintained in compression by pneumothorax, is very limited in extent and peripheral in location.

Alexander reports the following results from various clinics:

CLINIC	CASES	CURED	IMPROVED	UNCHANGED	DAMAGED	DIED (SOON OR LATE)
Sauerbruch (reported by Brunner)	14	2	3 + 2	1	1	5
Sauerbruch (reported by Sauerbruch)	26	15	3		2	1*
Gravesen	3†					1
Archibald	3					2
Stöcklin	30					2

In 22 of Stöcklin's cases the pneumothorax was given up because it was no longer needed or because it was unavoidably lost because of adhesions. Of the 22, 4 required a secondary thoracoplastic compression, 2 carried the pneumothorax, 1.5 and 5.5 years, respectively. The two deaths resulted from empyema secondary to pneumothorax.

* In 5 results unknown.

† In 2 pneumothorax was lost but did well.

From the foregoing it is evident that varying results have been obtained by different workers, that the possibility of a loss of the pneumothorax should always be borne in mind, although this does not appear to be any greater in this type of pneumothorax than in that employed without the assistance of thoracoplasty, and that should this occur there may be required a secondary major operation, which is always a possibility in connection with any induction of pneumothorax, but in this case, according to Davies, there is the added disadvantage of bone regeneration following the first operation.

A patient who has been under observation nearly one year, carrying an induced pneumothorax practically all of this time and on whom a thoracoplastic operation was performed in order to effect a collapse of the upper lobe, which had not been accomplished by the pneumothorax, furnishes the basis of this report.

Case report

C. R., age 33, married, steam-fitter by occupation. One sister died of pulmonary tuberculosis, but there was no apparent exposure of the patient. Father and mother are living. There is no other tuberculosis in the immediate family. In 1918 had "influenza," and again in 1920 while in California. There seems to be some question as to this diagnosis, for his physician is quoted as having stated that he thought he had "quick consumption." Cough and profuse sputum continued from three to four months but all cleared rapidly on removal to Arizona. A similar attack in 1922 was considered influenza, but from this the patient never recovered. During the succeeding two years he raised large amounts of sputum and suffered frequent and copious haemorrhages. The last of these occurred in September, 1924. He first came under my observation on December 2, 1924. There were cough, and elevation of temperature and pulse, and sputum in large amounts always showing tubercle bacilli. Weight 151 pounds; height 5 feet, 9 inches; highest weight, 182 pounds; average weight 160 pounds. The patient was well developed but poorly nourished. Examination of the chest showed marked dulness to the 4th rib anteriorly and to the 5th vertebral spine on the right, with prolonged expiration and fine râles throughout this area with cavity above the 2nd rib. The base of the heart and the great vessels were pulled to the right. The left lung appeared clear. Fluoroscopic examination and X-ray film (fig. 1) confirmed the foregoing. The sputum contained numerous acid-fast bacilli.

Pneumothorax was advised and first induced December 12, 1924. Negative to neutral pressures were maintained throughout, although the amounts introduced varied roughly from 400 to 800 cc., with as much as 1000 cc. used on two occasions without leaving a positive pressure at the termination of the

operation. By January 2, 1925, a collapse of about 60 per cent was produced (fig. 2), but this did not involve the apical cavity, which was held open by

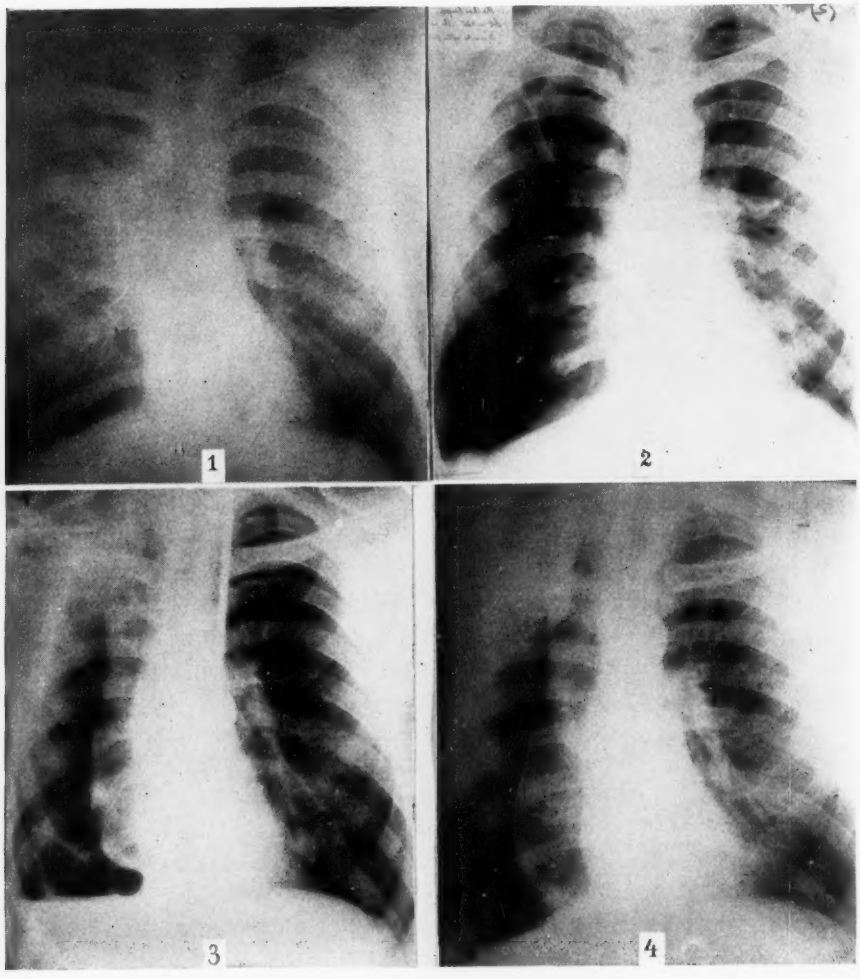

FIG. 1. BEFORE ARTIFICIAL PNEUMOTHORAX
FIG. 2. AFTER ARTIFICIAL PNEUMOTHORAX
FIG. 3. AFTER THORACOPLASTY
FIG. 4. FIVE MONTHS AFTER THORACOPLASTIC OPERATION WITH MAINTAINED PNEUMOTHORAX

adhesions to the axilla. Fluid was noted on January 21, 1925, and was absorbed quickly. This was again present on February 16, 1925, and was again absorbed.

By May 1, 1925, the patient had made definite improvement. The sputum had been reduced from about 15 to about 3 ounces daily. The temperature and pulse were normal and, while the weight was 146 pounds as compared with the initial weight of 151 pounds, the patient's principal complaint was of the cough. The signs were those of an induced pneumothorax in the base with an uncollapsed cavity at the apex.

By July it became evident that further attempts to collapse this portion by

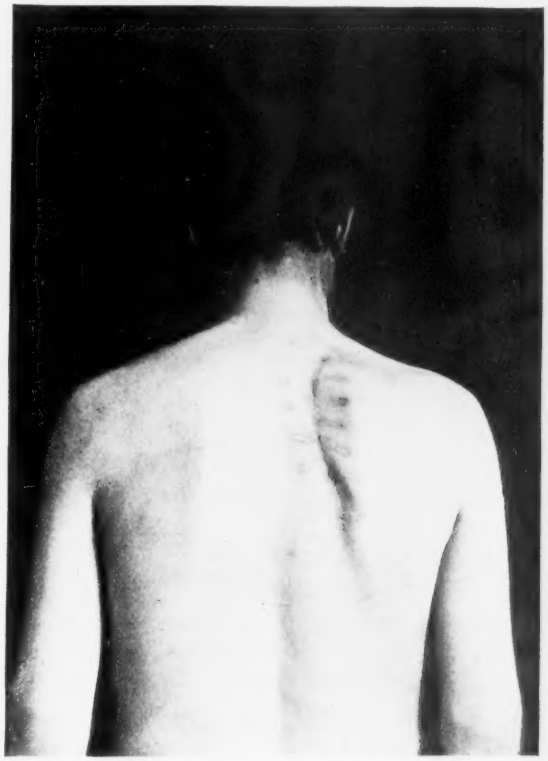

FIG. 5. PATIENT FIVE MONTHS AFTER THORACOPLASTIC OPERATION WITH MAINTAINED PNEUMOTHORAX

means of the pneumothorax would be futile, and a thoracoplasty was advised and accepted by the patient. At St. Joseph's Hospital, Denver, Dr. C. J. Lowen did a partial posterior thoracoplasty under paravertebral anaesthesia, removing portions of the upper six ribs. Prior to this operation the gas was allowed to absorb to a point at which the pleural surfaces appeared fluoroscopically to be nearly in apposition, in order to avoid undue intrapleural pressure shortly after the operation. The convalescence was uneventful and on August

15, 1925, the patient was admitted to the Jewish Consumptives Relief Society Sanatorium. It was not found necessary to introduce air during this period, the collapse of the apex having the effect of producing a greater amount of basal collapse. Fluid was noted at entrance in small amount (fig. 3), but this absorbed after the first refill. Since this time refills have been given every second week in amounts varying from 400 to 700 cc. The patient has been afebrile and ambulant, the cough is very slight, and the sputum varies from 2 to 4 ounces daily, and has been negative for tubercle bacilli 6 out of 8 times. The last examination showed an absence of râles on the right side. The weight at that time was 156 pounds (figs. 4 and 5).

It is too early to predict whether the pneumothorax can be continued as long as we may wish, whether fluid and subsequent adhesions may require a discontinuance of the pneumothorax, or whether, if this should be necessary, a later thoracoplastic operation will be needed, but we can state without possibility of contradiction that this patient was improved by the first incomplete pneumothorax, that this, however, was inadequate for the handling of the apical cavity, and that great improvement has so far resulted from the combination of induced pneumothorax and partial thoracoplasty.

Discussion by Dr. C. J. Lowen: The indications for the combined method are usually determined as in this case. It is only after an induced pneumothorax is insufficient because of adhesions over a cavity that it should be considered. The pneumothorax should also be, as Dr. Burnett mentioned, at least 50 per cent complete. There was a time when most writers were very enthusiastic about the combined method, but as their experience is increasing they are now recommending it only in selected cases. The advantages and disadvantages have been enumerated by the assigned, but there are at least two more drawbacks that should be considered in the general scheme of a decision. One is the lack of ideal immobilization in the combined method that is obtained with complete thoracoplasty, for, as a rule, regardless of the excellence of induced pneumothorax, the fluoroscope will demonstrate respiratory movements of the lungs. Another is the necessity of continued refills.

One of the reasons for intrapleural complications with this method is the possibility of perforation of the pleura or even the lung, which renders infection more liable when a large pleural space exists. When the disease is at the apex, removal of sufficient ribs to permit its collapse is all that is necessary. When in the lower lobe, rib resection and phrenicotomy are indicated. Care must be taken to deflate the pleural cavity to nearly zero before operation, or to choose a time when a refill is indicated because of likely complications. It should never be presented to the patient without his realizing the possibilities

of the necessity of complete thoracoplasty. Only in specific cases, such as this, for example, in which time has demonstrated insufficient air compression and a tolerant pleura, should it be used. Again, the combined procedures may be used in a patient too sick to submit to complete thoracoplasty, and yet allow sufficient improvement to permit it at some later date.

Note: (April 1, 1926) Since September, 1925, the sputum has failed to show tubercle bacilli, and the daily amount at present is from two to four drams. The patient's weight is 158 pounds. The temperature and pulse are normal. The patient is entirely free from symptoms.

PULMONARY ACTIVITY GREATEST AT THE APEX AND LEAST AT THE BASE[1,2]

JOSEPH WALSH

The typical or usual development of pulmonary tuberculosis is represented at necropsy by what is known as the *Laennec lung*, with fibrosis (the oldest lesion) at the apex, fibrocaseation below, and more recent scattered tubercles gradually becoming less in number to the base. Repeated physical examinations during life correspond with this appearance, making it evident that the clinical disease begins at the apex, and gradually descends. The extreme base is usually free from disease. The explanation of this manner of development in practically every textbook of pathology and clinical medicine is that the respiratory and circulatory activity of the lower lobe aid in preventing, and the inactivity of the upper lobe, especially the part above the first rib, predisposes to the development of tuberculosis.

While studying the pathology of tuberculosis, and keeping in mind the common manner of its development, I became convinced that contrary to this universal opinion, the apex is the most active part, and I presented some arguments for this opinion in a preliminary paper (1) one and a half years ago. In the meantime, further arguments and evidences have occurred to me; and, in addition, further study has shown that not only is the apex the most active part of the lung, but the base is its least active part. By activity I mean functional activity, comprising the air-pressure within and the degree of expansion of the individual alveoli, and the activity of the circulating blood.

My arguments are based on (1) therapeutics, (2) microscopic study of the size of the alveoli in normal lungs at different ages, (3) the manner of development of emphysema, (4) lack of protection at apex, (5) the appearances in chronic miliary tuberculosis, (6) anthracosis, (7) manner in which tuberculosis heals, (8) the locations of beginning clinical tuberculosis, (9) circulatory activity, (10) bacteriology, and (11) lymph flow.

[1] From the White Haven Sanatorium and the Laboratory of Postmortem Pathology of the Philadelphia General Hospital.

[2] Read before the Essex County Medical Society at Saranac Lake, New York, June 10, 1925, and the Pathological Society of Philadelphia, March 11, 1926.

1. Therapeutics: All our experience with tuberculosis goes to show that rest of an affected part is a definite aid toward cure, and modern treatment is based more on this than any other factor. The hip or knee-joint affected with tuberculosis is put absolutely at rest, and the frequency of cure makes it practically certain that the rest had a definite effect. The treatment of laryngeal tuberculosis by vocal rest is in the same category. The artificial-pneumothorax treatment of tuberculosis of the lungs is likewise postulated on it. If rest of a part, or the restriction of its activity, is in general, and even in the lungs, one of the best means of curing tuberculosis, we cannot also say that it is one of the best means for stimulating development.

To my mind this therapeutic argument is so strong as to be almost convincing by itself, that the practically constant affection of the apices points to their increased, and the usual freedom of the bases, to their decreased activity. In addition, this corresponds with what we see in other organs; for instance, Jones and Lovett (2) state that tuberculosis of the spine locates itself in the region of the greatest mobility (the dorsal lumbar), so that of 321 cases occurring in the dorsal region, only 71 were in the upper six, and 215 in the lower six vertebrae. In the mouth and respiratory tract tuberculosis occurs on active parts like the tongue, epiglottis, larynx and lungs, not in the nose and large bronchial tubes.

2. Microscopic Study of the Size of the Alveoli in Normal Lungs at Different Ages: This study showed that the alveoli are practically the same size throughout the lung of the newborn baby, and gradually increase in size with age, this increase being greatest at the apex and least at the base. The natural explanation is that the greatest respiratory activity is at the apex, and gradually decreases to the base, all our experience with organs being that increase in function develops increase in size, so that, when one kidney is removed (3) or one lung is extensively diseased, the other becomes larger. So true is this that at necropsy, when we find that the first kidney we reach is very much increased in size, we know before seeing the other that it will be very small, congenitally absent, or greatly diseased.

In this study, which was suggested by Dr. Joseph Sailer in 1920, and made at the Philadelphia General Hospital that year, and repeated in 1923, and again in 1925, normal lungs were half-inflated, then filled with 5 per cent formalin, and further inflated to what appeared to be full inspiration. Some of the lungs were inflated before removal from

the chest, so as to prevent overdistention. The lung was then hung either in 5 per cent formalin solution, or in an air-tight jar containing about an inch of pure formalin. After two days it was found sufficiently hardened in this condition of distention to cut sections from various parts without collapse.

Altogether, the lungs of three babies were studied; one fully developed stillborn, one of 2 days, and one of 4 months; and of four adults of 29, 46, 49 and 71 years of age. Stained microscopic specimens were made from sections of the upper lobe at the apex, at the mediastinal margin about the second rib, at the external lateral margin about the second rib, at the base anteriorly, and at the central interior portion about the third rib; of the lower lobe at the apex, the central interior portion about the angle of the scapula, the lower margin posteriorly, and the lower margin laterally. Sections were made from the right lung as well as the left in the child of 4 months, and in the adults of 49 and 71 years.

The findings were as follows: The alveoli were the same size throughout the lung of the stillborn baby (fig. 1) and the baby of 2 days; the alveoli at the apex were largest, and at the mediastinal margin second largest in the baby of 4 months, and elsewhere of the same size (fig. 2).

At the time I studied the lungs of the adults of 29 and 46, I was interested only in the fact that the alveoli at the apex were much larger than elsewhere, and made no illustrations of the alveoli at the extreme base. Since then my studies have led me to the conclusion that not only is the apex the most active part of the lung, but this activity gradually decreases to the base.

In the adult of 29 years the alveoli were largest at the apex, and larger at the central interior part of the upper lobe at about the third rib than at the lower margin of the upper lobe anteriorly at about the fifth rib. In the male of 46 years the inflation was not very successful, but in two

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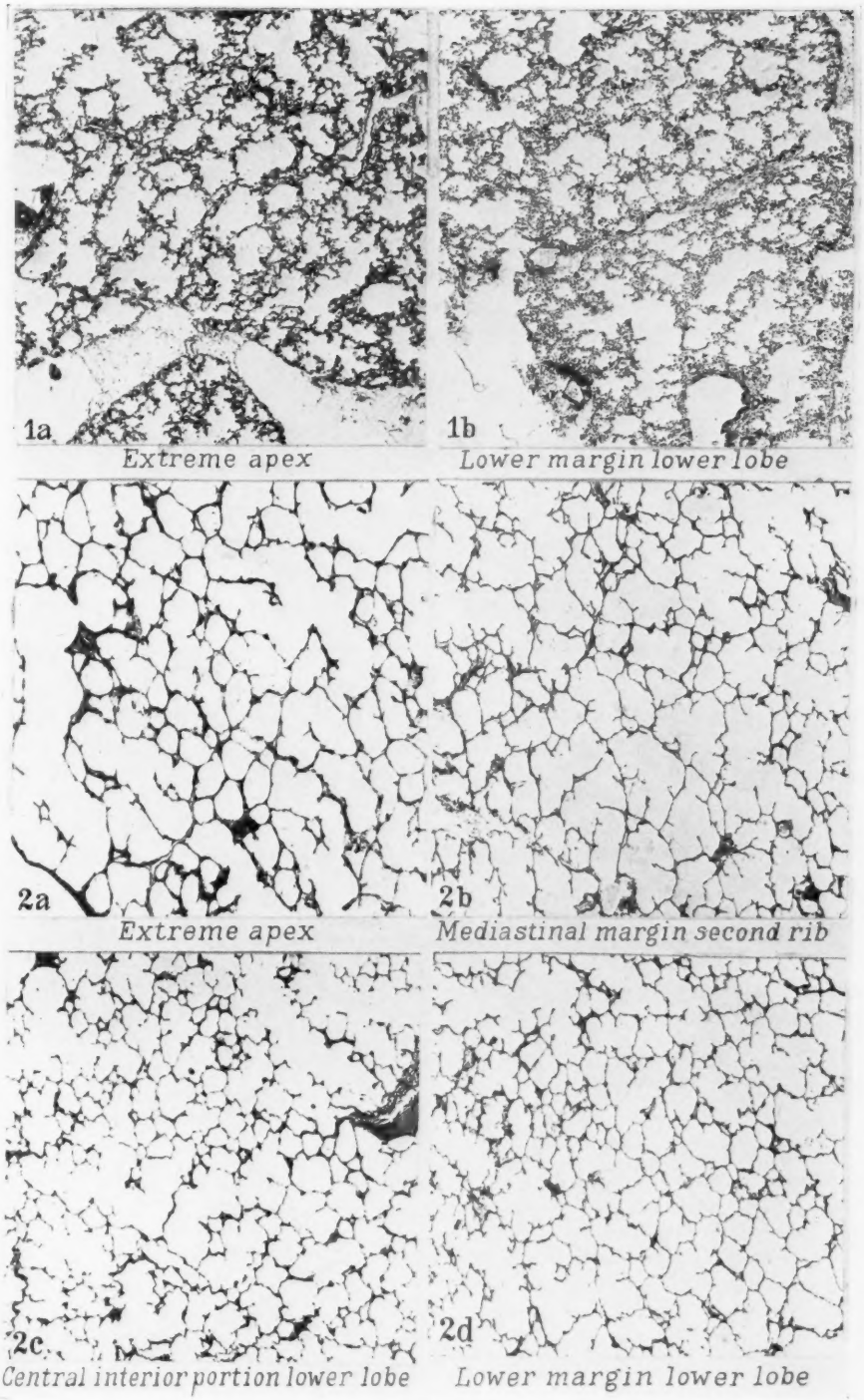
FIG. 1 a & b. LUNG OF STILLBORN, FULL-TERM BABY (P. G. H.). × 46

The alveoli appear about the same size, although the sections are from the extreme apex and extreme base on the surface of the lung. The numerous sections studied from other parts both on the surface and the interior, showed the alveoli the same size everywhere. (Photomicrographs by Cosner.)

FIG. 2 a, b, c & d. LUNG OF MALE, AGED 4 MONTHS (CASE NO. 10,108 P. G. H.). × 46

In the four sections shown the alveoli are the same size at the lower margin and at the central interior portion of the lower lobe, and larger at the mediastinal margin and at the apex. The numerous sections studied from other parts showed the alveoli the same size as those at the base. It appears that already at four months of age the over-respiratory activity of the upper part of the lung is evidenced by enlargement of the alveoli. (Inflated by Dr. Eorman, photomicrographs by Gosner.)



1a Extreme apex

1b Lower margin lower lobe

2a Extreme apex

2b Mediastinal margin second rib

2c Central interior portion lower lobe

2d Lower margin lower lobe

places which were perfectly satisfactory, namely, the apex of the upper and the apex of the lower lobe, the alveoli were larger in the former. In the male of 49 years, the alveoli at the base were evidently the smallest and the alveoli at the top of the lung evidently the largest, but at this top the alveoli at the apex and at the external lateral margin of the lung about the second rib were of the same size (fig. 3). The alveoli on the central interior portion of the upper lobe at about the third rib anteriorly were larger than those in the central interior portion of the lower lobe at about the angle of the scapula. This demonstrates that they decrease in size in the interior of the lung as well as on its surface. In the female of 71 years the alveoli at the apex were largest and at the base of the lung smallest, and those in between were smaller than the former and larger than the latter, but varied only a little among themselves (fig. 4).

I prepared the specimens of two babies and two adults; Dr. M. C. Borman, those of one baby and two adults. In addition, Dr. J. Howard Smith and a technician examined independently the microscopical specimens.

All four of us agreed that the alveoli in the lungs of the stillborn baby and the baby of 2 days were so uniform in size that it was impossible to notice any difference between them, and that they were already largest at the apex and second largest at the mediastinal margin in the baby of 4 months.

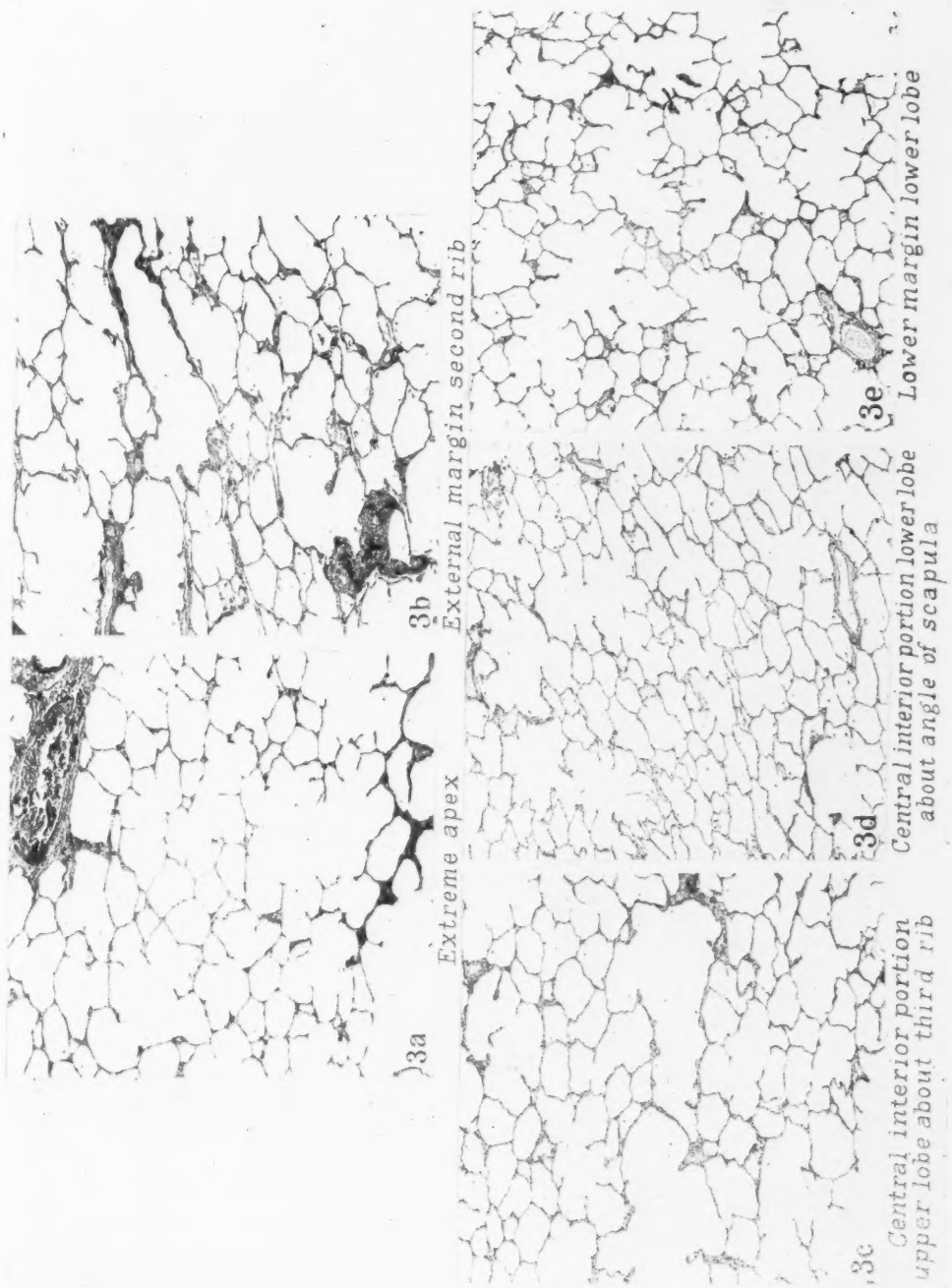
The agreement was also general that the size of the alveoli at the top of the adult lungs was definitely larger than below, and the alveoli at the base smaller than those above. We did not always agree on the exact succession of the alveoli intermediate between the base and the top.

In two adult cases sections were taken from both lungs. The right lung showed no appreciable difference from the left, and the middle-lobe sections corresponded with those from the middle of the left lung.

After noticing the marked difference in size, microscopically, between the alveoli at the apex and those at the base in the adult lung, I began to

FIG. 3 a, b, c, d & e. LUNG OF MALE, AGED 49 YEARS (CASE NO. 10,122 P. G. H.). × 46

In this case the size of the alveoli from largest to smallest was as follows: Apex, external margin at second rib, mediastinal margin at second rib, central interior portion at third rib, central interior portion of lower lobe at angle of scapula, and extreme base. It is to be noticed that the alveoli at the base were smaller than those in the interior of the lung at the angle of the scapula, in spite of the fact that the former were on the surface; in other words, the size decreased from above downward. In addition, the graduation in numerous specimens between the base and the top was even more evident than in these illustrations. (Inflated by Borman, photomicrographs by Gosner.)


3a
Extreme apex
3b
External margin second rib
3c
Central interior portion upper lobe about third rib
3d
Central interior portion lower lobe about angle of scapula
3e
Lower margin lower lobe

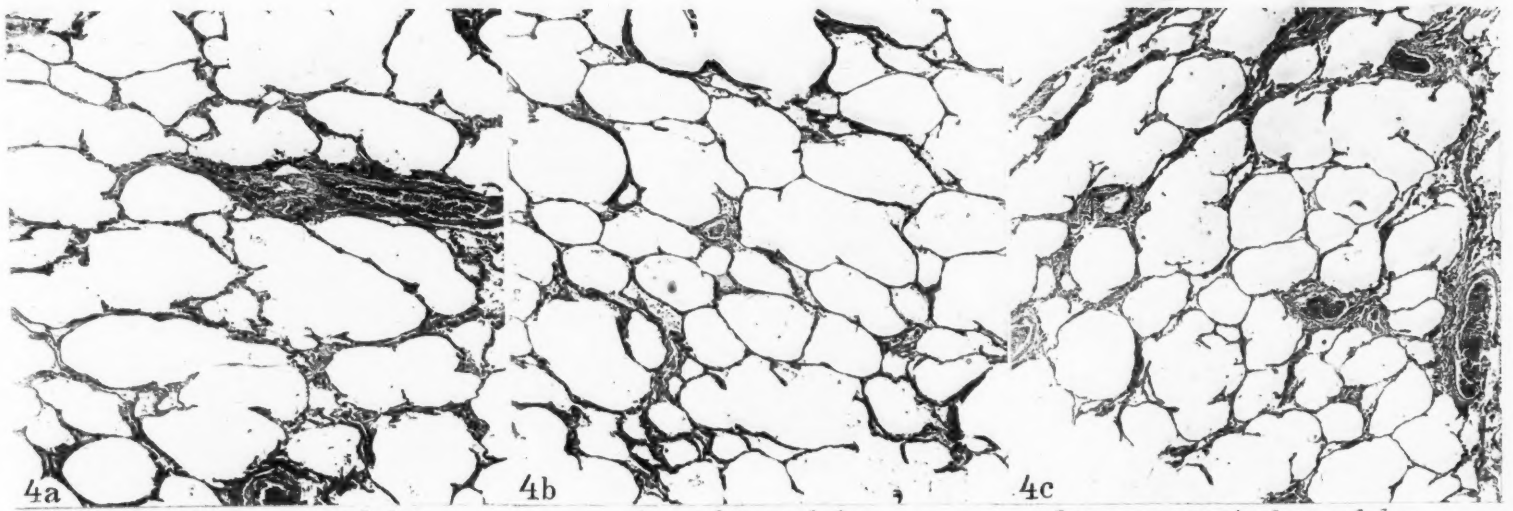


FIG. 4 a, b & c. LUNG OF FEMALE, AGED 71 years (CASE No. 10,052 P. G. H.). × 46

These three sections are from the outside of the lung, yet show the alveoli at the base smallest, apex of upper lobe largest and apex of lower lobe between. In some of the interior lung sections were found fibrous nodules with surrounding localized emphysema, and in a few others the alveoli were filled with exudate, making it impossible to place them in any sort of order. (Inflated by Borman, photomicrographs by Gosner.)

study the lungs macroscopically, just as they are removed from the body, and found that the larger size of the alveoli at the apex was demonstrable. This macroscopic demonstration is more evident when the lungs do not collapse spontaneously, and it is especially plain in cases of emphysema, even compensatory emphysema. To show it, a small portion of the lung should be pinched between the thumb and finger, in order to fill the alveoli with air and make them stand out.

From this study it was evident that the alveoli at the apex of the adult lung are largest in size and at the extreme base smallest. It appeared that the size gradually decreased from the apex to the base, with the exception that the alveoli on the outside surface are larger than on the interior of the lung at the same level, but the alveoli on the outside decrease in size gradually, and the alveoli on the interior show a similar decrease from top to bottom. Moreover, I am confident that some of the enlargement of the surface alveoli, in comparison with those in the interior on the same level, is a postmortem condition, due to the blood sinking to the back, away from the apical, anterior, and mediastinal surfaces especially, and the air rising to distend these abnormally.

Further, the size of the alveoli in between the top and bottom of the lung varies within sufficiently small limits for the manner in which the section is accidentally cut and petty local conditions to make a difference. For instance, even in what would be considered normal lungs a petty fibrous nodule is sometimes found by accident, with around it a petty localized area of emphysema. If the alveoli in this area are compared with ones above, which do not participate in the emphysema, they will be found larger. Conditions of this character were found in the interior of the lung of the female aged 71 years, making it difficult to decide on the relative size of the alveoli in this situation.

Likewise, in other cases studied, in which one lung was greatly contracted by fibrosis, and the other much enlarged by compensatory emphysema distending it across the sternum into the other side of the chest, I was inclined to think, from macroscopic appearances, that the alveoli at the mediastinal margin were the same size as, or occasionally even larger than those at the apex. This would lead me to believe that the greatest pressure of air is upward, and under normal conditions manifests itself at the highest point, but under abnormal conditions, when a point shortly below the apex is given special anatomical opportunity to expand, the overfunction is quite as noticeable here.

In the literature I have come across only two definite statements in

regard to the size of the alveoli; the first, that of Waters, in an elaborate monograph in 1860, which affirms the alveoli to be everywhere the same size; the second, that of Gray's *Anatomy* (Lea Brothers & Co., Phila., 1887, p. 937), which states that the alveoli are largest on the surface at the three margins and at the apex, and are smallest in the interior. It is quite evident that the first statement is wrong, and the second only partially correct, for it at least insinuates that the alveoli at the apex are large because they are on the margin, while in my study the alveoli on the margin at the base are the smallest, showing that it is not a variation between margin and interior, but between lower and upper part of the lung.

3. Manner of Development of Emphysema: The circumstance which led me originally to question the idea of the lessened activity of the apex in comparison with other parts of the lung, is the enormous distention, or even ballooning, of the apex sometimes seen in asthma and emphysema, in which a protrusion of the apex 1 to 2 cm. above its usual situation is not uncommon. In emphysema, the physical signs, the X-ray plate, and the necropsy, all show the alveoli at the apex to be more distended than elsewhere. It is particularly at the apex that we find the alveoli, postmortem, broken into one another in such numbers that they look like small bladders. Figure 5 shows such a condition at necropsy: the upper specimen is the extreme apex; the lower a part about an inch below the apex; the remainder of the lung showed a gradual decrease in size of the alveoli to the base.

This agrees in general with the different authorities, Kaufman (4) p. 280, Lord (5) and Norris and Landis (6) p. 535, who state that chronic vesicular emphysema begins at the upper part of the lung and spreads

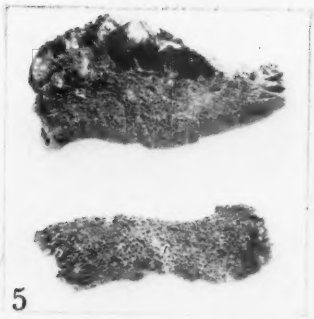
FIG. 5. LUNG OF MALE, AGED 42 YEARS (CASE NO. 5,171 WHITE HAVEN SANATORIUM) SHOWING CHRONIC HYPERTROPHIC EMPHYSEMA

The upper specimen is the extreme apex where numerous alveoli have broken down and run together; the lower, a part about an inch below the apex where the alveoli show more uniform distention; the remainder of the lung showed a gradual decrease in size of alveoli to base. (Natural size.)

FIG. 6 a & b. X-RAYS OF NORMAL AND MODERATELY EMPHYSEMATOUS CHESTS

In the first the lung is clearest at the base and less clear to the apex on account of the great thickness at the base accommodating more air; in the second the lung is least clear at the base and clearer to the apex on account of distention of the alveoli increasingly from the base upward. (Courtesy of Dr. Farrell, Jefferson Hospital.)

FIG. 7. TYPICAL EMPHYSEMATOUS CHEST SHOWING ENLARGEMENT POSTERIORLY AS WELL AS ANTERIORLY



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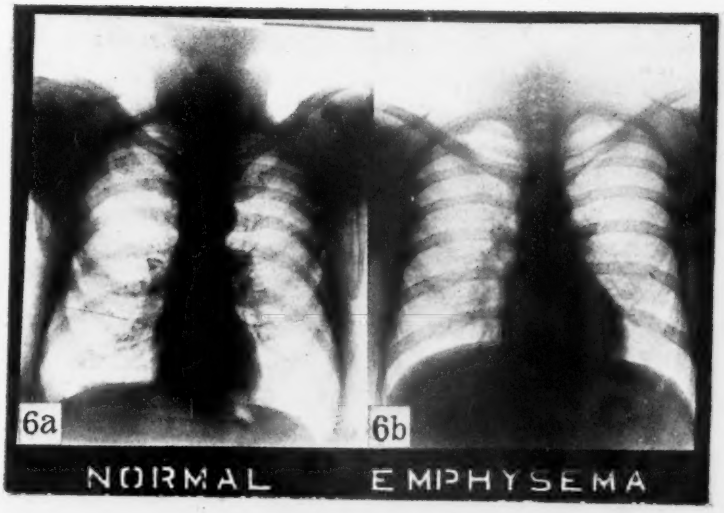
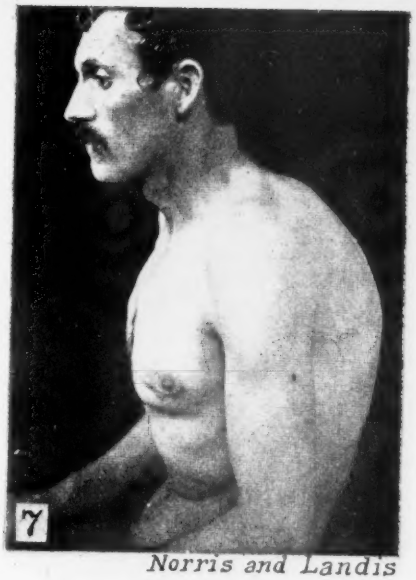




7

Norris and Landis

downward. Yet there is a tendency on the part of pathologists to describe it as most marked at the apex and the mediastinal and anterior borders, as though it was limited to these borders. This judgment is made from the appearance of the lungs on the necropsy table, and is only partially correct. What appears to be true is that the alveoli at the apex are actually ballooned on account of the breaking of the walls and the running together of a number of alveoli, while immediately below they are more regularly distended, and from this point are gradually less distended to the base, except that the alveoli in the interior are not quite so distended as the alveoli on the surface at the same level. In other words, there is a gradual decrease in size of the alveoli on the surface of the lung from the apex to the base, and also a gradual decrease of the alveoli interiorly from the apex to the base.

The reason for the pathologist's statement is that just before and after death the blood sinks to the back of the lung, compressing the alveoli on the posterior surface, and the air rises to the front, ballooning the alveoli on the anterior surface in a fashion not existing before the fatal disease. Careful examination of the emphysematous lung shows the appearance I have described.

The accompanying X-ray (fig. 6) corresponds with my description, and illustrates its truth even in moderate emphysema. The first picture represents a normal lung showing the lung clearer from the apex to the base, on account of the fact that the latter is so thick in comparison with the former and contains, therefore, so much more air. In the second picture the opposite appearance is found, namely, the lung is least clear at the base, and gradually clearer to the apex on account of distention of the alveoli increasingly from the base upward, making the walls at the apex so thin as to be scarcely visible.

The appearance of the emphysematous chest clinically (fig. 7) also confirms my statement. It enlarges gradually from the apex downward, posteriorly as well as anteriorly. If, in emphysema, the alveoli at the apex are first to distend, and even rupture into one another, and the alveoli at the base are the last to show these appearances, the evidence is very great that it is because they are the most active at the apex and less active downward.

4. Lack of Protection at the Apex: Not only do the physical signs and necropsies demonstrate overexpansion of the apex in comparison with the rest of the lung, but macroscopic anatomy shows the apex to be the

least protected part of the thorax. In its external aspects the lung is surrounded by a bony cage and transverse muscle fibres except at the apex, where it expands upward between vertically placed muscles (fig. 8). On the sides of the chest there is no opportunity for the lung to protrude between the ribs, on account of the transversely placed intercostal muscles and the up and down movement of the lung, which changes at every instant the relation of the lung to the chest-wall. At the apex the expansion is not confined by transverse muscle, and, with no lateral

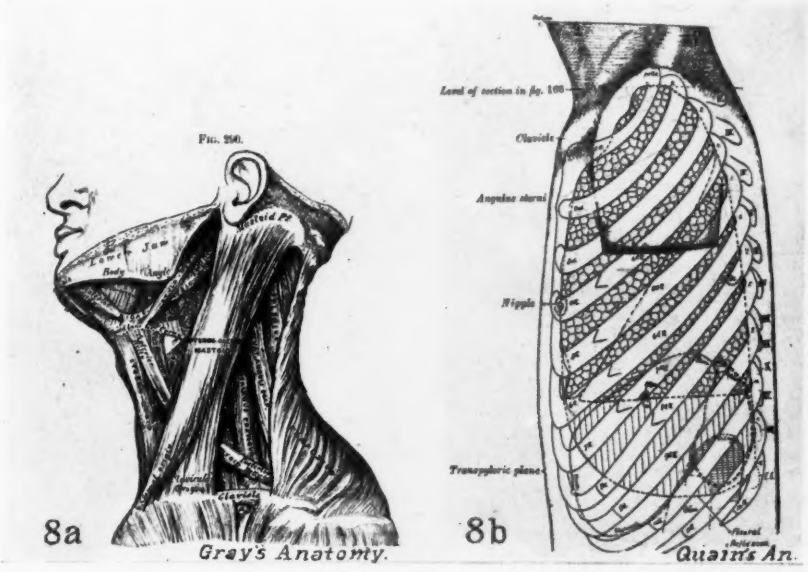


Fig. 8 a & b. Showing Where the Apex Expands Upward between Vertically Placed Muscles in Order to Demonstrate Its Lack of Protection

motion to the lung, the expansion occurs constantly in the same place, allowing easily a sort of hernial protrusion. Kaufman (4) p. 280, Beitzke (7) and Norris and Landis (6) also call attention to the lack of protection in this situation.

In my preliminary paper (1) I made a special point of this idea, but I have gradually come to see that it is more of local than of general importance. The pressure of air is upward to such a degree that, even if the apex were better protected, the lung would still find its way through, especially under abnormal conditions. Look, for instance, at what happens in severe emphysema: not only does the apex protrude, but the entire upper part of the chest is distended (fig. 7).

It still remains true that this lack of protection at the apex aids in allowing the apical alveoli to become larger than they would if protection were afforded, as is evident from the enlargement of the lung across the mediastinum, when the other lung is retracted by disease, but we see constantly a possibility of expansion of the base downward under even normal conditions without it taking place, thereby showing that it is not opportunity to expand which is the important factor, but the actual amount of air-pressure. Cunningham (8) tells us, "During respiration the thin inferior border moves freely in a vertical direction within the phrenico-costal sinus, but even after the deepest breath it never reaches the extreme lower limit of this recess."

From our experience with pneumothorax, we know that in the case of great air-pressure at the base the diaphragm everts in order to produce greater space. This eversion is apparently almost within physiological limits, since it is frequently accompanied by no symptomatology and, when the pneumothorax cures, the diaphragm returns to normal. In respiration not only does the diaphragm not evert, but, according to Cunningham, it does not descend even to its possible normal limit, while at the apex, with time, the alveoli distend and push even through tissue designed to hold them. Surely the pressure of air is upward, not downward.

5. The Appearances in Chronic Miliary Tuberculosis: In typical bilateral hematogenous miliary tuberculosis, when the patient lives long enough for the tubercles to develop in size, they are largest at the apex, and gradually lessen to the base. Tendeloo (9) says, "In chronic miliary tuberculosis we see small nodules occurring in the midst of larger ones, in general the size becoming smaller in a cranio-caudal direction." And Ribbert, quoted by Tendeloo (10), even affirms they are sometimes absent at the base. Figure 9 represents three cases in order to demonstrate the commonness of this type. The gradual lessening in size and number from the apex downward is easily seen.

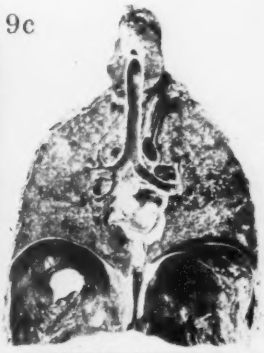
In these cases of hematogenous miliary tuberculosis, we have every reason to believe that tubercle bacilli were distributed reasonably uniformly throughout the lungs. The result shows a development of tubercles practically everywhere, but larger and more numerous gradually upward. This demonstrates that a certain number of tubercle bacilli located in the base failed to develop, and apparently even died, and gradually upward more of them developed, and developed much faster.

It also demonstrates that the part above the first rib is only the most susceptible because the entire lung is gradually more susceptible upward, not because of any association with the first rib.

9a

(Beitzke in Aschoff's Path. Anatomie)

(Tendeloo, Sixth Int. Cong. on Tuberculosis)



(Fig. 20, Graff und Kupferle)

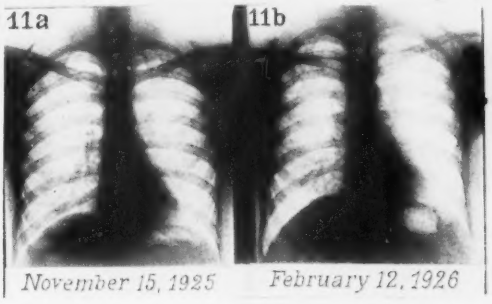


FIG. 9 a, b & c. DISTRIBUTION OF TUBERCLES IN CHRONIC HEMATOGENOUS MILIARY TUBERCULOSIS SHOWING DECREASE IN SIZE AND NUMBER FROM ABOVE DOWNWARD

FIG. 10. PRIMARY "AFFECT" IN FORM OF CALCAREOUS NODULE TWO FINGER-BREADTHS FROM EXTERNAL MARGIN IN LOWER PART OF RIGHT UPPER LOBE

Typical situation would be nearer pleura. The large white patches in both lungs are photographic defects, both lungs being practically normal.

FIG. 11 a & b. X-RAYS OF CASE WITH BREAKDOWN OCTOBER, 1925, FOLLOWED BY IMPROVEMENT

The plate of November 15, 1925, shows infiltration of both apices especially the left with scattered tubercles below; that of February 12, 1926, clearing up of the shadows from below upward. (Courtesy of Dr. McCutcheon.)

What is the cause of this gradually increasing susceptibility? The answer which occurs at once is a possible dependence on functional activity, either less or more. If the former, then we must believe that

chronic emphysema begins at the apex on account of diminished functional activity in this region, and, when the lower lobe enlarges (becomes emphysematous) following disease of the upper, it is due not to increased but diminished functional activity, which is absurd. No! it is impossible to get away from the evident fact that as the lower lobe enlarges on increase of its functional activity due to disease of the upper, so the upper part of the lung is the first to enlarge with age and in chronic emphysema on account of its being the most active.

If the area above the first rib were as much more susceptible than the rest of the lung as the advocates of Freund's theory assert, we would expect to see the tubercles in this situation much larger, and not only as large as corresponds with gradual increase from the base up.

The paradox has been proposed by Krause (11) to account for early involvement of the apex and subsequent frequent cure, that tubercle bacilli settle there on account of its lack of motion, and the tuberculosis cures more easily because of this immotility. If this were true, we ought to find in a chronic miliary condition the tubercles at the apex smaller than elsewhere. They are neither larger nor smaller than we would expect considering my idea true, namely, that the predisposition of the apex to implantation and development of tubercle bacilli is on account of it being the most active part of the lung, and this activity, and therefore, the predisposition to tuberculosis, gradually decrease from the apex to the base.

6. Anthracosis: The distribution of coal dust in the lung at the necropsy table usually corresponds with my conception, namely, in greatest amount at the apex, and gradually less to the base. Beitzke (7), and many others, have noted the same thing. This distribution is accounted for by the greatest air-pressure being upward, with, therefore, greater likelihood of the particles being carried upward. In addition, the greater activity of the alveoli makes it easier for them to gain entrance to the lymph-channels.

7. Manner in Which Tuberculosis Heals: The lower the tuberculous lesion, the more common the cure. This is demonstrated by the results of the two early manifestations of tuberculosis in the lung, (1) the primary "affect," which is usually in the midlung toward the periphery (fig. 10), and which usually heals; (2) the first clinical manifestation, which is usually at the apex, and heals much less frequently. So true is

this that these two lesions might be defined as, (1) the lesion of curable, and (2) the lesion of advancing tuberculosis. Since activity is the greatest stimulator of progression and inactivity the best means of cure, this points to activity as least below and gradually greater upward.

On account of the fact that the typical widespread chronic tuberculosis of the lung shows at necropsy a greater amount of fibrous tissue in the upper part of the lung, it is sometimes thought that tuberculosis cures from above downward; yet, in clinically healing tuberculosis, the physical signs, like râles and the roentgen-ray shadows, disappear from below upward, in other words, the cure is evidently in this direction.

Figure 11 represents the roentgen-ray plates of a physician who had an acute breakdown with hemorrhages last October. The physical signs showed tuberculous infiltration of both apices, as evidenced by dulness, bronchial breathing, etc., and scattered tubercles below, as evidenced by widespread moist râles. On rest and nourishment the patient gained twenty-three pounds, the symptoms disappeared, and the râles cleared up from below, being present now only above the second rib. The X-rays taken at Mont Alto Sanatorium show, on the plate of last November, infiltration at both apices, especially the left, and scattered small shadows simulating a snowstorm to the base; on the one taken in February the snowstorm shadows below have cleared up, though the shadows at the apex remain.

To explain the appearance of chronic tuberculosis at necropsy we must bear in mind how it occurs. The first manifestation is at the apex, and in the ordinary resistant, in other words, chronic case, there is a tendency for the lesion to heal, and more or less fibrous tissue occurs around it. Further lesions are the result of crops of tubercles appearing time and again below the original lesion, and one, two, or three of these successive crops may show more or less cure with the development around them of more or less fibrous tissue. Of course, every time there is cessation of activity with attempt at cure, all parts of the diseased area proceed to fibrose, and the already existing fibrosis has an opportunity to become denser. The lesion at the apex being the oldest, the fibrosis is densest. Eventually there occurs a larger or smaller crop of tubercles, on account of which the patient dies.

At necropsy the last crop will show no cure or fibrosis, and the crops above an amount of fibrosis increasing toward the apex, which took place in the past. The greater amount of fibrosis at the apex is only because this lesion has been curing a longer time than the lesions below, and

composed, as it is, of fibrous tissue with obliterated blood-vessels and bronchial tubes, it is not so susceptible to later infection.

Concretely, we might state a case in which the first crop of tubercles at the apex occurred six years before, the second crop three years before, and the last crop two weeks before death; the last will show no healing or fibrosis, the second some, and the first or apical crop considerable.

8. The Locations of Beginning Clinical Tuberculosis: Though the majority of cases of chronic pulmonary tuberculosis show the first clinical manifestation above the first rib near the termination of the paravertebral bronchus, the minority, which begin at the termination of the first

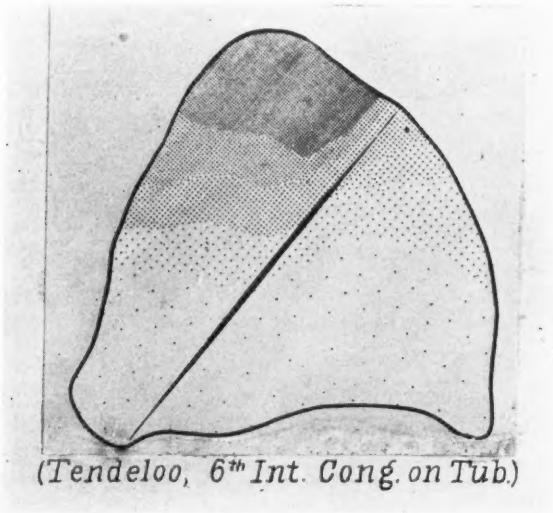


FIG. 12. DIAGRAM OF PROBABLE LOCATION OF FIRST FOCI IN CLINICAL TUBERCULOSIS, THE SITE OF PREDILECTION BEING IN PARAVERTEBRAL CRANIAL PART AND DIMINISHING RAPIDLY IN ALL DIRECTIONS

interspace bronchus below the first rib, is quite considerable (12), and particularly restricted activity of the part above, as described by Freund (13) and others, could have no influence on these beginnings. Allowing increased activity from the base up to be the factor determining the frequency of disease at the apex, permits ready explanation of disease inception to be gradually less to the base.

On account of the statement that the part above the first rib is more susceptible because it is confined by the first rib, the large number of

cases in which tuberculosis begins shortly below the first rib is overlooked. This is partly the result of the confusion between the clinician and pathologist in the accurate defining of the apex, allowing the part above the first rib to be given credit for more than its share of tuberculous manifestations. Speaking of the apex clinically, we mean that part above the clavicle, and therefore, the first rib, while the anatomical and pathological definition of the apex is the upper fifth of the lung. This upper fifth includes the lung to the second rib anteriorly and fourth posteriorly, allowing the clinician to assume that the disease began above the clavicle whenever the pathologist states it began at the apex. The apex of the lung is described by the anatomist Quain (14) "as reaching down to a horizontal plane corresponding to the second costal cartilage and junction of the manubrium with the body of the sternum in front and the disc between the fourth and fifth thoracic vertebrae behind." This is the entire upper lobe posteriorly and the upper third arteriorly.

Tendeloo (9) has given us a diagram of the frequency of the beginning tuberculosis in all situations (fig. 12). This diagram shows practically four areas, the first comprising about the anatomical apex, which is about twice as large as the small area above the first rib; the second comprising the remainder of the upper half of the upper lobe, and the apex of the lower; the third extending to the middle of the lung; and the fourth taking in the entire lower half of the lung. In other words, Tendeloo makes the entire anatomical apex equally or almost equally susceptible, and if this is true the first rib has no relation to susceptibility. I am willing to allow that the part above the first rib is the most susceptible, but only to that degree more than the part immediately below that would correspond with gradually increasing susceptibility from the base up. In the lower part the diagram corresponds exactly with my conclusions, in that the manifestations become so few below the midlung (in other words, below the entrance of the bronchus), that they may be considered accidental, the natural location being above, because, even when the bacilli are scattered, the ones in the upper half, no matter what their location, are more likely to develop, on account of its overfunction, and the ones in the lower half less likely to develop on account of lessened activity. Instead of insisting so much on the susceptibility of the apex, I would prefer to teach that the lung is susceptible to tuberculosis in an increasing degree from the base to the top.

I was inclined to think, at first, that this overactivity of the apices pointed strongly to inhalation infection, because overfunction means in

the lung greater suction with greater air velocity, making for greater capability of carrying bacilli upward, but the appearances found in chronic miliary tuberculosis show that, even when infection is by the circulation, and bacilli are distributed everywhere throughout the lung with the production of tubercles, the latter are more likely to heal at the base and continue to develop at the apex, leaving eventually an apical lesion, which in its later progress may give the appearance of a "Laennec lung."

That this sometimes occurs is evidenced by necropsy findings, which show the upper part of the upper lobes with chronic disease, the adjacent part with more recent disease, and one or both lower lobes apparently normal, until careful study demonstrates mild fibrosis in strands or petty nodules pointing to the likelihood of previous widespread tubercles in these lower lobes which have healed.

9. Circulatory Activity: Tendeloo (10), Beitzke (7) and many others assert that the active flow of blood is greatest at the base and least at the apex; hence, the more likely development of tuberculosis at the apex. This statement appears to me contradicted by pathological facts. Edema and passive hyperemia (hypostatic pneumonia) are essentially associated with sluggishness of the circulation, and they invariably begin at and are frequently limited to the posterior lower part of the lung, suggesting that the circulation is weakest, or least active, in this situation.

In the second place, according to Calmette (16), it is in the very vascular organs that the bacillus develops most readily, and according to Kolodny it develops in other organs, not at the site of least, but of greatest blood supply; for instance, Kolodny (15) states:

> A macro- and microscopical anatomical study of the blood supply of the skeleton reveals an interesting parallelism between the frequency with which certain skeletal regions are involved in tuberculosis, and the richness of their blood supply. This parallelism is proved in relation to the *sulcus bicipitis humeri, epicondyli femoris, collum* and *caput femoris*, to the acetabulum and to the vertebrae."

In the meninges tubercles occur at the base, where the blood supply is greatest, not over the convexity where it is least. Lupus develops most frequently in the skin of the face, the part of the skin with the richest blood supply. Heart disease associated with damming back of the blood in the lungs is, if anything, rather antagonistic to than provocative of tuberculosis.

With these examples before us, we cannot allow that tuberculosis occurs at the apex on account of its lessened blood supply without the most positive proof. In fact, after consideration it appears to me that the site of predilection for the development of tuberculosis in an organ is where it is physically most active and physiologically has the greatest blood supply. And, remembering the fact that in the cure of tuberculosis Nature throws an impenetrable wall about the lesion, thus preventing the ingress of oxygen or blood, the inference is plain that the posterior basal margin of the lung is the least frequently affected because of its little functional activity, both as regards the entrance of air and the passage of blood.

10. Bacteriology: An argument, not infrequently stated, is that the diminished aeration of the apex, produced by its lessened activity, favors the development of tubercle bacilli. This argument is contradicted by their growth on artificial media, and by the manner of cure of tuberculosis. Tubercle bacilli are aerobic, not anaerobic. On artificial media they grow with predilection on the surface, so that even when planted in the interior they come to the surface for development. In addition, Nature's method of cure is by cutting off the blood supply to the part, and throwing an impenetrable wall about the lesion, thus preventing the easy ingress of oxygen, and while the lesion is thus closed it heals without great difficulty, but when a cavity forms in the lung, its wall continues to act as a breeding place for tubercle bacilli indefinitely. The fact that they develop better at the apex than elsewhere in the lung is surely not a proof of less aeration of the part.

A comparison of the two most common diseases of the lung, lobar pneumonia and tuberculosis, supports my contention. Pneumonia has a predilection for the lower, tuberculosis for the upper lobe; the pneumococcus is aerobic, but optionally anaerobic; the tubercle bacillus is distinctly aerobic. Pneumonia is frequently associated with arteriosclerosis and heart disease, which have a tendency to produce edema and passive hyperemia of the lower lobe, conditions which interfere with the aeration and circulatory activity of the part; in other words, lack of aeration and stagnation of the circulation predispose to pneumonia; tuberculosis is so uncommonly associated with arteriosclerosis and heart disease as to allow the idea of an antagonism between them, and passive hyperemia is even used as a cure. If we are to judge from the bacteriology, therefore, we would expect more oxygen and more circulatory activity in the upper lobe.

This explanation also shows at once why chronic hypertrophic emphysema, in spite of its excessive respiratory activity, is almost never associated with tuberculosis, because it is also accompanied by passive hyperemia, due either to heart disease or overwork of the heart.

11. Lymph-Flow: Tendeloo (10) says the lymph-flow is most active at the base and least active at the apex. I am personally unable to confirm or deny this, but I am willing to think that it is not proved. He affirms that tubercles develop at the apex rather than at the base, because when tubercle bacilli are scattered widely throughout the lung they linger at the apex on account of the decreased lymph circulation failing to carry them away, while at the base they are washed out by the free flow of lymph. He has not, however, told us whither they are washed. Is it to the hilum lymph nodes? Apparently not, since the lymph nodes draining the unaffected bases are free of tubercles, or, at least, are freer than the lymph nodes draining the tuberculous parts. Do they pass through these lymph nodes into the right heart and again through the lungs, and thus repeatedly until eventually all the bacilli have accumulated at the apex? He does not say. I do not know whether the lymph-flow is greater at the base or at the apex, but my idea is that, on account of the lessened respiratory function of the lower parts of the lung, when tubercle bacilli gain entrance they produce little or no damage and eventually die.

Tendeloo gives the same explanation for the failure of anthracosis at the base, namely, that the anthracotic granules are washed away by the free flow of lymph. Whither are they washed? If to the lymph nodes at the hilum, then those draining nonanthracotic parts ought to show more anthracosis than lymph nodes above; just the opposite is true. My idea is that on account of the lessened activity at the base, they are not so likely to reach the ultimate lung unit, and especially the alveoli where entrance to the tissue would be easy, but settling on the wall of bronchial tubes they are later expectorated.

My understanding of tuberculosis is: That the bacilli of a primary "affect," whether this is under the skin or in the lung, or at the apex, base, or midlung, where it usually is, are picked up by the lymph-vessels and carried to the nearest lymph nodes, where they produce a lesion; the bacilli of the secondary manifestation are not picked up by the lymph-vessels at all. This being true, it matters not whether the lymph drainage is greater or less, tubercle bacilli will not be washed out by it.

CONCLUSIONS

1. The functional activity of the lung is greatest at the apex and gradually diminishes to the base, where it is least. This conclusion is based on the therapeutic action of rest, on the increasing development in size and number of hematogenous miliary tubercles from the base upward, the enlargement of the alveoli in emphysema and in normal lungs with age in the same direction, and on the fact that, while the inferior border of the lung fails to descend as low as nature would allow it, the apex is pushing upward through tissues designed to hold it.

2. On account of the pulmonary activity being greatest at the apex and gradually less to the base, the development of chronic pulmonary tuberculosis in the form of the "Laennec lung," of chronic hypertrophic emphysema and of anthracosis, is more readily understood. In addition, something is added to the pathogenesis of lobar pneumonia in that it develops by predilection in the part of the lung where the respiratory activity is least and the circulation more readily becomes stagnant.

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THE CHEMICAL STUDY OF BACTERIA

XI. THE DEVELOPMENT OF A SYSTEMATIC ANALYTICAL METHOD FOR THE COMPARATIVE STUDY OF BACTERIAL CELLS[1]

TREAT B. JOHNSON

The primary object of this paper[2] is to have permanently on record for future reference an outline of the experimental procedure or technique, which has been developed and followed by the workers in this laboratory in their study of the chemistry of tubercle bacilli. As we are engaged in a pioneer development, it must not be assumed that it is possible for us to present at this stage of our work a complete and entirely satisfactory plan of analysis. While our technique may be modified in many ways as the investigation is continued and new facts are acquired, the outline will serve, in its present form, as a key to future papers by my co-workers, several of which are now being prepared for publication. It will also meet a valuable service in that it will aid and simplify the problem of correlating the results of our researches with those of the workers in other fields, who are coöperating with us in the study of this most interesting subject. All experimental data, which have been revealed as a result of the different researches, will be discussed in our future papers.

The first publications from this laboratory dealt largely with the study of the nucleic acid of tubercle bacilli. Our present investigation has been confined to a study of the protein fractions, and the outline will serve to show our general method of attack. In our future work, attention will be paid to the nonprotein nitrogenous constituents of the cell, and also the lipoid and cholesterol fractions of tubercle bacilli.

[1] From the Department of Chemistry, Yale University.

[2] This paper is the eleventh of a series of publications dealing with the chemistry of bacteria, in which are recorded the results of an extensive chemical research on cells now being carried on in the Sterling Chemistry Laboratory of Yale University. The referenes to previous reports and papers are as follows: Johnson and Brown, *Proc. Nat. Acad. Sci.*, 1922, viii, 187; *Jour. Biol. Chem.*, 1922, liv, 721, 731; *Amer. Rev. Tuberc.*, 1923, vii, 285. Brown and Johnson, *Jour. Amer. Chem. Soc.*, 1923, lvii, 199. Johnson, *Amer. Rev. Tuberc.*, 1924, x, 473; *Tr. Nat. Tuberc. Assoc.*, 1925, 374. Johnson and Coghill, *Jour. Biol. Chem.*, 1925, lxiii, 225; *Jour. Amer. Chem. Soc.*, 1925, xlvii, 2838. All the work on tubercle bacilli has been supported by grants from the National Tuberculosis Association; and the plan here outlined has been prepared in coöperation with the Medical Research Committee of that organization.

THE POSSIBILITIES AND DIFFICULTIES OF APPLYING ORGANIC CHEMISTRY TO THE STUDY OF BACTERIA

Professor F. G. Donnan[3] of England once made the following statement during a conversation on the future development of chemistry:

> That looking into the future of chemistry he could see only two paths which were likely to lead to the opening up of vast fields of knowledge. They appear at first widely divergent, but some day they will converge and with startling results. The first is the investigation of the structure of the atom and molecule, and the second is the study of the chemical processes of the living cell.

While this statement smacks of the nature of a prophecy, it is an expression of a very general opinion among scientific workers to-day, who visualize the future developments in biochemistry. If one may judge from the advances being made in chemical science at the present time, it seems safe to predict that our future increase of knowledge will be acquired by two entirely different methods of attack. The elucidation of the fundamentals of chemistry will be aided through the application of the principles of higher mathematics. Consequently, we may look to the physicist as the chief contributor of new knowledge bearing on the structure of atoms and molecules. For the development of the field of biochemistry the biological sciences will turn to the organic chemist for new definitions and interpretations of natural phenomena. These sciences have not advanced to that stage at which the non-mathematical method of attack is unproductive. There is still to be learned in this field much of a fundamental nature, that may yet be interpreted in terms of the ingenious conception of the structural molecule, which has made organic chemistry an exact science. The biologist, and more recently the bacteriologist, have finally come to realize that it is not the physical changes of cells or bacterial organisms observed under high magnification that are the most important characteristics of their history, but that the compounds of carbon and nitrogen, which they secrete or absorb in their life processes, demand the very closest attention.

It was as late as 1885 that the physiologist looked upon probably 90 per cent of the organic materials of cells or living tissue as organic constructions of unknown composition and structure. Preceding that time most of the fundamental organic changes occurring during life were enshrouded in mystery. To-day the complex organic combinations of

[3] Journal Soc. Chem. Ind., 1924, xliii, 667.

carbon, such as the fats, sugars, proteins, tannins, alkaloidal principles, terpenes, animal and plant pigments, purines and pyrimidines have been revealed in their true nature by the researches of organic chemists, and now those complicated constructions, the starches and celluloses, are also beginning to yield their secrets. Notwithstanding these advances, we are still a long distance from the goal; but when we look back to the state of our knowledge previous to 1900 we are forced to admit that the developments of recent years in this field of science are nothing short of marvelous.

Up to the present time we have gone hardly beyond the initial step of a general survey of the intricate problems dealing with the structure of living cells. Our present technique does not allow us to apply an analytical method without destruction of the life of the cell. Of the various organic combinations that have been shown to function universally in cell structure none has received more attention by organic chemists than the proteins; yet how uncertain we are, and how inaccurate or inexact is our knowledge to-day of the molecular structure of these important compounds. The proteins thus far examined by chemists have been separated from dead cells, and are, therefore, from a biological point of view, inert. In what fundamental way the characteristic proteins of living cells differ from the proteins isolated from dead cells we are not yet able to say.

When the writer began the present investigation on tubercle bacilli, and undertook to develop a technique whereby it would be possible to make an application of organic chemistry to the study of bacteria, he realized that he was encountering a very complex and most difficult problem. The knowledge of the chemistry of these microörganisms was very fragmentary, and it is still far from exact. No procedure or systematic method of chemical attack had been developed by previous workers which promised any possibility of utilization for the development of a precise research or plan of approach. Knowing, as we now do, that the composition of a cellular organism endowed with such metabolic activities is very complex, that we are dealing with a complicated organization of colloidal systems, and that every organic constituent of the cell operates or functions in all its reactions under the influence of colloids, it seemed many times very doubtful to the writer, during the early stage of this research, whether the organic chemist will really be able to accomplish much by making this attack on Nature's domain, and whether his aim to accomplish beneficent results is completely justified.

A spirit of optimism regarding future possibilities, together with the knowledge that all advances in chemical thought and methods have generally been accomplished by putting questions or speculations to the test of experimental proof in the laboratory, has served to counteract what has been mentioned above to discourage a chemical attack in this field. The results thus far obtained have amply rewarded us for our efforts. We have opened up a new vista in chemical bacteriology, leading to rich fields for future study. The major difficulty that the writer foresees, which will restrict rapid progress in research, is the inability of the organic chemist to obtain bacteria in sufficient quantity for chemical research. It is now an acknowledged fact that the biologist and bacteriologist cannot make further progress without a knowledge of the chemical processes influencing the mechanism of cell reproduction and growth. Such knowledge will not be acquired by restricting attention to a study of the physical structure of bacteria and to their mode of propagation.

THE DEVELOPMENT OF A PROCEDURE FOR THE PROXIMATE ANALYSIS OF BACTERIA

In order to make a distinct contribution to methods of chemical procedure which are applicable in bacteriological research, and to obtain data which will increase our present knowledge of the chemistry of tubercle bacilli, our problem first resolved itself into one of developing a practical laboratory technique for analyzing the cells. To be of real service this should enable one to obtain not only specific data, but it must also fulfil certain conditions that need to be maintained if the results of analytical research of this character are to have any practical or theoretical significance. These specifications are as follows: (1) Conservation of the constituents of the bacterial cells in their original form and avoidance of all autolytic changes; (2) maintenance of the sterility of the cell fractions during analytical operations, and avoidance of the use of reagents which interact with the cell constituents; (3) making possible the successful application of a scheme of proximate analysis, whereby the cell constituents can be separated into simpler groups or fractions; (4) adoption of procedures offering no difficulty of application in the hands of different workers; and (5) be productive of such data as can be safely used to indicate marked chemical differences in the composition of cells, and thereby make the analytical method of attack one of practical utility for the comparative study of cells.

The successful carrying out of our plan called for a knowledge of the strain of microörganism employed, of the conditions affecting its growth on a large scale, the character of the media used for growth, the method of separating bacteria from culture media after growth, and the treatment applied before shipment of bacteria from the factory or plant to the laboratory. It was also necessary to have a complete control over the method of desiccation before subjecting to any chemical treatment. One treatment, the results of which have undoubtedly led to errors in the work of some previous workers, is that of autoclaving before or after desiccation of bacteria. It is known from experience that autoclaving leads to decided alterations in the composition of the cell. All of these factors influence indirectly in some degree the results of our chemical work, and it is for this reason that we have incorporated in our outline the whole history of the bacteria from the time of their growth in the factory to the final stage of cell dissection or end of our scheme of proximate analysis.

The method of operating, which is outlined, has made possible the separation of characteristic cell constituents into fractions which can be purified and studied further. The procedure outlined has proved also of special service in our study of distribution of nitrogen, and it has enabled us to make sharp separations of water-soluble and water-insoluble proteins and other nitrogenous fractions. The characteristic differences between these substances will be discussed in papers to be published in the near future. For the running down of cell constituents possessing specific biological activity the appended outline (see chart) has served a

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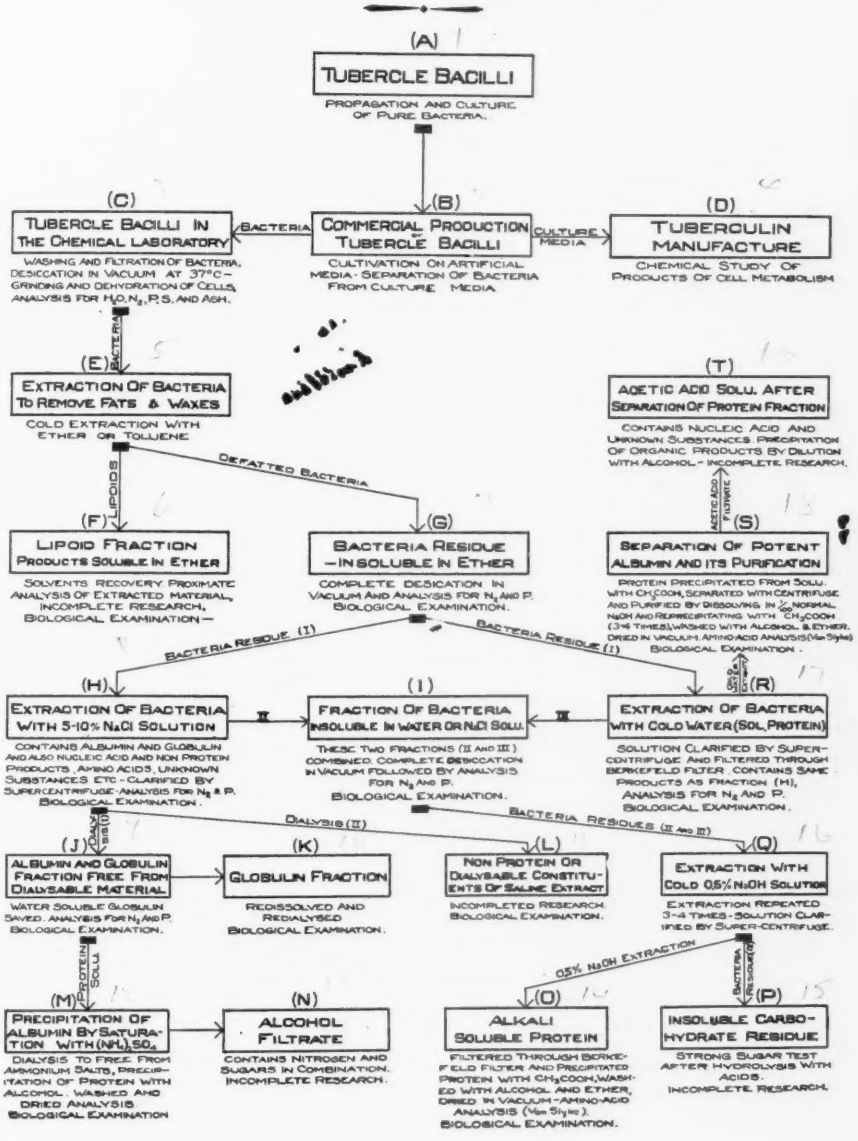
Brief Explanation of Chart Illustrating Method of Chemical Study

The solution of the problem of developing any method of chemical analysis applicable to bacteria is made very difficult on account of their complex nature. Our primary object has been to work toward a more systematic chemical method of investigation than hitherto applied. Instead of dealing with the properties of closely related organic compounds, in which case questions of separation and purification are not troublesome, we have the difficulty, in the analysis of bacteria, not only of obtaining substances in a pure state, but also of separating certain major fractions of unrelated substances into units to which it is possible to make an application of more refined methods of analysis. The chart represents, therefore, a procedure of proximate chemical analysis only, in which different fractions containing specific substances are partially separated and made available for more refined research. The specific units in our scheme of separation of cell constituents are designated alphabetically (*A*, *B*, *C*, etc.) and under each unit is indicated briefly the special treatment that has been applied for purification and separation of specific organic substances.

A completed study of each fractional unit involves an independent research. In order to follow the division of the various organic constituents of the cell and locate them, we have traced their course by following analytically the distribution of nitrogen and phosphorus. These are the only two elements that can be followed analytically with any accu-

A CHEMICAL STUDY OF TUBERCLE BACILLI

NITROGEN AND PHOSPHORUS DISTRIBUTION


(A)
TUBERCLE BACILLI
PROPAGATION AND CULTURE OF PURE BACTERIA.
(B)
COMMERCIAL PRODUCTION OF TUBERCLE BACILLI
CULTIVATION ON ARTIFICIAL MEDIA - SEPARATION OF BACTERIA FROM CULTURE MEDIA
BACTERIA
CULTURE MEDIA
(C)
TUBERCLE BACILLI IN THE CHEMICAL LABORATORY
WASHING AND FILTRATION OF BACTERIA, DESICCATION IN VACUUM AT 37°C - GRINDING AND DEHYDRATION OF CELLS, ANALYSIS FOR H2O, N2, P, S, AND ASH.
(D)
TUBERCULIN MANUFACTURE
CHEMICAL STUDY OF PRODUCTS OF CELL METABOLISM
BACTERIA
(E)
EXTRACTION OF BACTERIA TO REMOVE FATS & WAXES
COLD EXTRACTION WITH ETHER OR TOLUENE
(T)
ACETIC ACID SOLU. AFTER SEPARATION OF PROTEIN FRACTION
CONTAINS NUCLEIC ACID AND UNKNOWN SUBSTANCES. PRECIPITATION OF ORGANIC PRODUCTS BY DILUTION WITH ALCOHOL - INCOMPLETE RESEARCH.
LIPOIDS
DEFATTED BACTERIA
ACETIC ACID FILTRATE
(F)
LIPOID FRACTION PRODUCTS SOLUBLE IN ETHER
SOLVENTS RECOVERY. PROXIMATE ANALYSIS OF EXTRACTED MATERIAL, INCOMPLETE RESEARCH, BIOLOGICAL EXAMINATION —
(G)
BACTERIA RESIDUE — INSOLUBLE IN ETHER
COMPLETE DESICATION IN VACUUM AND ANALYSIS FOR N2 AND P. BIOLOGICAL EXAMINATION.
(S)
SEPARATION OF POTENT ALBUMIN AND ITS PURIFICATION
PROTEIN PRECIPITATED FROM SOLU. WITH CH3COOH, SEPARATED WITH CENTRIFUGE AND PURIFIED BY DISSOLVING IN 1/20 NORMAL NaOH AND REPRECIPITATING WITH CH3COOH (3-4 TIMES), WASHED WITH ALCOHOL & ETHER, DRIED IN VACUUM. AMINO ACID ANALYSIS (Van Slyke) BIOLOGICAL EXAMINATION.
BACTERIA RESIDUE (I)
BACTERIA RESIDUE (I)
(H)
EXTRACTION OF BACTERIA WITH 5-10% NaCl SOLUTION
CONTAINS ALBUMIN AND GLOBULIN AND ALSO NUCLEIC ACID AND NON PROTEIN PRODUCTS, AMINO ACIDS, UNKNOWN SUBSTANCES ETC - CLARIFIED BY SUPERCENTRIFUGE - ANALYSIS FOR N2 & P. BIOLOGICAL EXAMINATION.
II
(I)
FRACTION OF BACTERIA INSOLUBLE IN WATER OR NaCl SOLU.
THESE TWO FRACTIONS (II AND III) COMBINED. COMPLETE DESICCATION IN VACUUM FOLLOWED BY ANALYSIS FOR N2 AND P. BIOLOGICAL EXAMINATION.
III
(R)
EXTRACTION OF BACTERIA WITH COLD WATER (SOL. PROTEIN)
SOLUTION CLARIFIED BY SUPERCENTRIFUGE AND FILTERED THROUGH BERKEFELD FILTER. CONTAINS SAME PRODUCTS AS FRACTION (H). ANALYSIS FOR N2 AND P. BIOLOGICAL EXAMINATION.
DIALYSIS (II)
BACTERIA RESIDUES (II and III)
(J)
ALBUMIN AND GLOBULIN FRACTION FREE FROM DIALYSABLE MATERIAL
WATER SOLUBLE GLOBULIN SAVED. ANALYSIS FOR N2 AND P. BIOLOGICAL EXAMINATION.
(K)
GLOBULIN FRACTION
REDISSOLVED AND REDIALYSED BIOLOGICAL EXAMINATION.
(L)
NON PROTEIN OR DIALYSABLE CONSTITUENTS OF SALINE EXTRACT
INCOMPLETED RESEARCH. BIOLOGICAL EXAMINATION.
(Q)
EXTRACTION WITH COLD 0.5% NaOH SOLUTION
EXTRACTION REPEATED 3-4 TIMES - SOLUTION CLARIFIED BY SUPER-CENTRIFUGE.
PROTEIN SOLU.
0.5% NaOH EXTRACTION
BACTERIA RESIDUE
(M)
PRECIPITATION OF ALBUMIN BY SATURATION WITH (NH4)2SO4
DIALYSIS TO FREE FROM AMMONIUM SALTS, PRECIPITATION OF PROTEIN WITH ALCOHOL. WASHED AND DRIED ANALYSIS. BIOLOGICAL EXAMINATION
(N)
ALCOHOL FILTRATE
CONTAINS NITROGEN AND SUGARS IN COMBINATION. INCOMPLETE RESEARCH.
(O)
ALKALI SOLUBLE PROTEIN
FILTERED THROUGH BERKEFELD FILTER AND PRECIPITATED PROTEIN WITH CH3COOH, WASHED WITH ALCOHOL AND ETHER, DRIED IN VACUUM - AMINO-ACID ANALYSIS (Van Slyke). BIOLOGICAL EXAMINATION.
(P)
INSOLUBLE CARBOHYDRATE RESIDUE
STRONG SUGAR TEST AFTER HYDROLYSIS WITH ACIDS. INCOMPLETE RESEARCH.

valuable purpose. Each specific fraction can be reserved for a special biological research and a complete history given of its source. The work, in general, is thus less empirical in character. In this way it is possible to keep a complete record of the experimental results, and trace out their true significance. An endeavor has been made to develop a practical plan whereby one may correlate the results of different workers in the same field.

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racy, and a knowledge of their distribution is practically the only guide we have at present for locating and detecting specific organic combinations containing these elements.

In the scheme outlined we have utilized water only for extraction. We have purposely avoided extractive processes that depend on alcohol. The question whether the bacterium contains alcohol-soluble proteins is to be decided by future research. The solvents used, besides water, have been those such as ethers, toluene, etc., which dissolve fat and waxes, and have practically no solubility effect on protein combinations. If one applies our procedure to autoclaved and unautoclaved cells very marked chemical differences will be detected in the individual fractions, indicating fundamental changes brought about by heating.

According to our method of cell-analysis the most potent protein constituent is located in unit *S*. This represents a water-soluble albumin of high biological activity, but present in small amount only. In most of the processes hitherto applied for extraction of protein principles from tubercle bacilli this fraction has not been isolated because the autoclaved cell has been used. This protein is coagulated on heating. The major proportion of the proteins in tubercle bacilli is insoluble in water. This is carried in our process to unit *O*, and extracted with alkali. This protein is entirely different from the fraction found in unit *S*, both biologically and in amino-acid content. In unit *M* is found the same protein that functions in unit *S*, but carried through a process of purification which makes it free from globulins. The globulin fraction revealed in unit *K* is very small indeed.

In this work emphasis has been placed on the proteins and their relationship to the tuberculin reaction. Consequently, biological tests were applied in conjunction with our analytical operations. In fact, the result of these biological tests served, in many cases, in properly coördinating our analytical procedures. Under the various units is indicated where biological examinations of our material were made. The results of these tests, when brought together and coördinated with our analytical scheme, should reveal facts of great interest and importance.

Under some units we have indicated where we have not completed our outlined research. In fact, each unit opens up new problems for study. The question of distribution of sugar and other carbohydrate combinations has not been considered in our preliminary work. Our scheme has revealed to us, however, where we are to look for such material. The study of sugar combinations will be taken up as our work progresses. Especially important is unit *L*, which contains over one-third of all cell-nitrogen. One of our major problems this coming year is to determine the nature of the nitrogen constituents of this unit.

In conclusion, it should be kept in mind that the plan of chemical analysis outlined in the chart, if applied systematically, will enable us to reveal fundamental chemical differences in bacteria brought about by heating, changes in composition of culture media and other conditions influencing the life processes of the cell. All the bacteria used by us were grown on artificial media.

In the carrying out of a large research enterprise of the character of this investigation of tubercle bacilli and bringing it to a successful conclusion, it is very essential that some plan be adopted whereby the accomplishments of the various workers engaged may be properly valued. If the publication of this outline or scheme of chemical procedure will serve as an aid for the proper coördination of the results and ideas of the various workers active in this joint research, the writer will feel that he has done a true service, and feel repaid for constructing this paper.

THE EFFECT OF BETA-RAYS ON BACTERIAL GROWTH[1,2]

C. H. BOISSEVAIN

Campbell and Wood (1) discovered in 1906 that potassium and rubidium emit β-rays. These are the only two elements of low atomic weight that show radioactivity. All the other radioactive substances, uranium, thorium and their offspring, have very high atomic weights. The biological importance of potassium has been known for a long time and Ringer knew that the potassium of his solution could be replaced by rubidium, but it was only in 1916 that Zwaardemaker and Feenstra (2) connected this with the radioactivity of these two elements. An isolated frog's heart that is perfused with physiological sodium-chloride solution stops beating after a short time, but if we perfuse it with Ringer's solution that also contains potassium chloride, sodium carbonate and calcium chloride, it will continue its contractions during a long period. Zwaardemaker and Feenstra found that the potassium in this solution could be replaced by equiradioactive amounts of rubidium, uranium, thorium or radium. If the necessary quantity of potassium is 55 mgm. per litre of solution, this could be replaced by 105 mgm. Rb, 15 mgm. U, 24 mgm. Th or 3.10 mgm. Ra. The heavier radioactive elements do not seem to replace the potassium as completely as does rubidium.

Zwaardemaker is of the opinion that a physiological antagonism exists between the α-rays that consist of positively charged helium atoms and the β-rays that consist of negatively charged electrons. Perfectly pure uranium or thorium emit only α-rays, but they are continuously transformed into uranium X and mesothorium, which emit β-rays. They, in their turn, change continuously into uranium II and radiothorium, which again emit α-rays. The disintegration period of uranium X and mesothorium is very short, and it is practically impossible to obtain a product that produces only β-rays, and it is accordingly difficult to prove this hypothesis.

[1] From the laboratory of the Colorado Foundation for Research in Tuberculosis at Colorado College, Colorado Springs, Colorado.

[2] Read before the medical section of the Southwestern Division of the American Association for the Advancement of Science, Phoenix, Arizona, February, 1926.

Zwaardemaker's results were attacked by Hamburger (3), who showed that it is possible to keep a frog's heart beating in a solution that does not contain potassium or any other radioactive element, but an excess of calcium. The heart muscle may, however, possess a sufficient store of potassium to enable it to function when its irritability has been changed by the addition of calcium. Zwaardemaker showed that the presence of adrenalin decreases the potassium requirement of the heart and that the hearts of summer and winter frogs require a different potassium concentration to function. β-Rays are a stream of electrons, and differ in no respect from any other electric current, and any physical or chemical stimulus that causes an electric current, through chemical reaction or otherwise, may have the same effect as the presence of potassium atoms. Under these conditions it seems a hopeless undertaking to try to settle the importance of the β-rays of potassium by means of experiments with perfusion of the heart.

It is different when we study the effect of minerals on bacterial growth in synthetic media. Here we can control the composition of our medium, and the only foreign elements introduced are the bacteria themselves, but we can reduce this by inoculating only a few bacilli that have been washed in distilled water, and by serial transplants in the same medium. Raulin (4) already knew in 1869 that potassium was necessary for the development of bacteria; Nägeli (5) and Benecke (6) found that rubidium and caesium could replace potassium in the culture medium for *Aspergillus niger*. These experiments lost much of their value when Fermi (7) showed that aspergillus grows in distilled water containing only ammonium lactate. The minerals that diffuse from the glass are apparently sufficient; Fermi even claims to have grown aspergillus in his solution in metal containers. Conditions are different with the tubercle bacillus, which is extremely exacting in its requirements as regards the culture medium. In addition to nitrogen and carbon it requires potassium, magnesium and phosphorus (8). Calmette (9) observed that its growth is much favored by the addition of small amounts of iron. The influence of radioactive salts on the development of tubercle bacilli was studied by Becquerel (10) and Frouin (11). They found that small amounts (0.04 mgm. per cc.) of uranium and thorium salts have a favorable effect on the growth of the bacillus. There was, however, only a little difference between the flasks with the radioactive salts and the controls. Frouin (12) found that the salts of other metals, notably those of vanadium and of some of the rare-earth metals, favored the growth of the tubercle

bacilli. All these experiments were performed with culture media that contained potassium, and no effort was made to find whether any of these metals could be substituted for potassium or any of the other salts.

I chose Long's synthetic medium (13) to study the question of the replacement of potassium by other elements in the culture of the tubercle bacillus. Potassium chloride and sodium phosphate were substituted for the potassium phosphate of the original solution, which enabled me to substitute the other alkali chlorides. The medium had the following composition:

	grams
H_2O	100.—
Asparagine	0.5
Na_2HPO	0.3
Ammonium citrate	0.5
Na_2CO_3	0.15
$MgSO_4$	0.1
KCl	0.2
Ferrous ammonium citrate	0.005
Glycerine	4.—

Other media were made, containing no KCl, or, in its place, equimolecular amounts of lithium-chloride, sodium chloride, rubidium chloride, caesium chloride, 40 mgm. of vanadium chloride or 0.2 mgm. uranium chloride. Each flask was inoculated with a loopful from a thin veil of human tubercle bacilli (Gray 2) on glycerine-broth. The surface of the broth containing KCl was covered with a fairly thick veil after three weeks' incubation, and the flask that contained rubidium chloride showed even more abundant growth. The surface of the medium containing uranium was covered with a thin veil, weighing less than one-tenth as much as that in the flask with potassium chloride. None of the other flasks showed any growth at all. Serial inoculations in new flasks containing rubidium or uranium showed the same growth as the original flasks. Virulence tests were performed with the bacilli after the third transfer, and the guinea pigs died after the same interval (3 months) as the controls, which had been inoculated with bacilli grown on Long's medium.

Although vanadium chloride cannot replace potassium it can replace the iron; the bacilli grow abundantly and with undiminished virulence on media containing rubidium and vanadium instead of potassium and iron. Henri suggested, in the discussion of Frouin's paper in the Société de Biologie, that the favorable effect of vanadium might be due to the

fact that vanadium and the rare-earth metals, which also favor development of the bacilli, all show several degrees of oxidation. The fact that vanadium can replace iron certainly makes this explanation more probable. But no such explanation is possible in the case of rubidium. Caesium and rubidium are chemically very closely related and extremely hard to separate. One of them, however, favors the growth of the tubercle bacillus even more than potassium does, and the other is without any effect. These results suggest that the β-rays of potassium and rubidium may have some importance. It is interesting to investigate whether calcium can replace potassium; calcium causes a precipitation in Long's solution, which cannot be used for this purpose. Up till now I have not succeeded in composing a medium without potassium and with calcium upon which the tubercle bacillus will grow.

It seems curious that elements with β-radiation are necessary for the life of the tubercle bacillus, when we remember that it is killed by the action of ultraviolet light. This light causes the emission of photoelectrons from the atoms according to Einstein's equation:

$$\frac{m\,v^2}{2} = h\nu - P$$

where m = mass of electron, v_1 = velocity of electron, h = Planck's constant, ν = vibration number of the light, and P the work that is necessary to leave the surface of the irradiated substance. If we neglect this last quantity we can calculate the maximum velocity of a photoelectron. For ultraviolet light of a wave-length of 3000 Å we find that this velocity is 1000 km. per second. The β-rays of potassium show many different velocities and these have not been determined exactly. It seems strange that the electrons of potassium have not the same destructive effect on the tissues that the photoelectrons of the ultraviolet radiations have. Potassium, however, will kill bacilli when nitrogen is absent. Dr. Eric Webb found in our laboratory that potassium ions are toxic for colon bacilli and staphylococci in salt-solution suspensions. He poured plates containing 1 cc. of a suspension of colon bacilli in physiological salt solution at one-hour intervals, counted the colonies, and found a steady decrease in their number. This decrease became much greater when 0.02 per cent of KCl was added. We find thus that potassium is toxic for bacteria in the same concentration that it is favorable for their development. Perhaps it will be possible to demonstrate that very small doses of ultraviolet light are also favorable for the growth of bacilli

and that there is only a quantitative difference between the action of ultraviolet light and potassium. All our cultures are continuously exposed to the γ-rays derived from the radium emanation in the atmosphere and to the cosmic rays, whose wave-length was recently measured by Milliken. Their combined effect is, however, only $\pm$ 1/100 of that of the β-rays from potassium and probably without effect on fast-growing microörganisms. But here we enter the domain of pure speculation which it is safer to avoid.

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CERTAIN HISTORICAL AND EPIDEMIOLOGICAL OBSERVATIONS ON TUBERCULOSIS[1]

DONALD B. ARMSTRONG[2]

The ambitious title originally suggested by your Program Committee for this paper was *The History and Epidemiology of Tuberculosis.* Large volumes have been written on these subjects, and the title seemed to constitute too extensive an order for a single lecture as well as for the qualifications of the speaker. Consequently, we have arbitrarily limited the field on the epidemiological side to certain observations on phases of the subject that are perhaps of special interest to the medical practitioner. On the historical side, we shall not bore you with dates and details, familiar as you already are with the outstanding events in the history of the disease.

In general terms, we might perhaps first recall the extremely interesting metamorphosis through which the science and art of public health and disease control have passed during the last century or so. Out of the Dark Ages of the Eighteenth Century came a general sanitary awakening, characterized by what has been described as a "shot-gun" sanitation, applying empirically certain more or less incidental findings bearing upon the general limitation of communicable disease through the media of improved water supplies, waste disposal, etc. There then followed a more specific and rational application of knowledge to disease control, based on the findings of bacteriology, and leading to the development of the general science of epidemiology. While overlapping to some extent in point of time, there succeeded, in a general way, a widening range of developments in the field of immunology and, on top of all this growth, has come the modern application of personal hygiene, of individual responsibility for disease control and health promotion, with the development of health education in its various disease-suppressing and health-promoting phases.

Tuberculosis has been a major consideration in the last few phases of

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this evolution. Some of the earliest work in bacteriology involved this disease. Certain of the first studies in epidemiology were concerned with tuberculosis, and while relatively little has been accomplished, compared with successful efforts in connection with other diseases, nevertheless the history of attempts to develop artificial methods of immunization against tuberculosis covers a longer period of time and a wider variety of experimental attack than can be said to be the case for any other disease. Then, finally, in this development of public health education the interest in tuberculosis has led the way into the field of personal hygiene.

An indication of the intricacy of the tuberculosis problem is to be found in the contrast between how little we actually know with reference to this disease with certainty as compared with how much we know concerning certain other diseases, such as, for instance, typhoid fever and diphtheria. In diphtheria we know its cause, its transmission, its cure, and its prevention. In tuberculosis we, of course, do know its bacterial cause, and we also are able to list a host of unweighted social, economic, racial, and hygienic etiological factors. But one still finds substantial differences of opinion as to the usual age of infection, as to the relative importance of methods of spread, and as to the significance of generalized community-wide tuberculization and the bearing of this upon immunity. Yet, while there are many uncertainties compared with simpler disease problems, contributions are constantly being made to our knowledge of tuberculosis. Research laboratories are telling us more and more about the essential characteristics of the tubercle bacillus. We are constantly learning additional facts about the reaction of the human organism to tuberculous infection. Unsuccessful as have been past efforts aimed at the development of a specific immunological procedure, yet recently events have taken place, and demonstrations have been made, which are, to say the least, promising in this direction. Furthermore, and this is perhaps the chief contribution of the last decade or two to the problem, we have learned much in recent years concerning the social aspects of the disease. We have gained some idea, though perhaps not an accurate one, as to the relative influence of indirect etiological factors of an economic and social character. Incidentally, we have also to some extent unlearned some of the generally accepted assumptions with reference to social influences on the tuberculosis problem prevalent in the early part of the present century.

It appears that we are just at present outgrowing a period characterized

by a tendency to exaggerate the importance, so far as tuberculosis is concerned, of certain unsightly and perhaps indecent so called unsanitary environmental factors related to living problems, and especially housing. We have come more lately to recognize the superior significance of individual and personal *methods* of living as compared with *equipment* for living. As we shall point out later, there is no question about the importance of overcrowding, congestion, and similar factors tending to increase contact. But how about certain other conditions sometimes much emphasized, such as dirty backyards, the accumulation of refuse, improper garbage disposal, etc.? The relatively new art of teaching and practising personal hygiene has led us to realize that more important than these environmental factors are personal methods of living, including not only diet, but cleanliness, respiratory hygiene, positive health habits, and similar health-promoting considerations. We were told by the promoters of a decade or two ago that "germs lurk in dark, damp places," and we thought of unsightly and ill-smelling cellars, or refuse-clogged air-shafts. We still believe that "germs lurk in dark, damp places," but we think of infected tonsils, gall-bladders, intestines, and carious teeth. We have learned that ignorant or careless human pigs in a palace will frequently have a higher sickness and death rate than clean, intelligent human beings in a hovel. The possession of an advantageous race-stock will also very materially help the human beings in a hovel, especially in their fight against tuberculosis.

We have learned that personal hygienic living is important in that, while it perhaps does not very materially decrease the amount of infection in tuberculosis, it does increase resistance to active tuberculous disease. We have learned that the incidence of active tuberculous disease is affected by air, exercise, cleanliness, food, diet, economic, social, and occupational conditions; by efforts at the early detection of the disease; by familiarity with the incipient signs of the disease; and by prompt and adequate medical and institutional care. The Framingham Demonstration, carried out over a period of seven years in that Massachusetts town, was essentially an experiment to determine the effectiveness of certain broad measures of social control, and resulted in a reduction in the tuberculosis death-rate during this period of seven years from 121 deaths per 100,000 to 38.

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in Egyptian mummies at least three thousand years old. Greek and Roman literature indicates that tuberculosis was one of the commonest diseases among these peoples. It is said that it was known to Hindoo physicians long before the Christian Era. Yet, it is important to realize that there were many countries in the world practically free from the disease, such as the interiors of Africa and Australia, and the Islands of the Pacific, until tuberculosis, with the so called benefits of civilization, was carried to these territories by the tuberculized white man.

However, as stated previously, it is not our intention to discuss this phase of the subject in any detail. It would seem to be more serviceable to study, briefly, the course of the disease in recent times in a typical urban community with which we are all familiar, such as the City of New York. Such a review may at least produce certain general observations and perhaps epidemiological side-lights applicable to the disease as we find it elsewhere to-day.

Tuberculosis, or consumption, has played a conspicuous part as a death factor in New York City for as long a time as we have any records. There is, for instance, in existence a semicentennial table of mortality, the first available mortality records for the City, presenting the causes of death from 1804 to 1853. In this tabulation we find that in 1804 there were 499 deaths from consumption, or a rate or 667 per 100,000. By 1832 the rate had dropped to 628, and by 1853 to 469. In contrast to these high rates, the rate for 1925 for New York City was 88 per 100,000, which includes all forms of tuberculosis, whereas the figures cited for the previous years are those for so called consumption only, and do not include "white swelling," "scrofula," etc. So recently as 1915, the death-rate in New York City for tuberculosis was 196 per 100,000. In 1868 the death-rate for pulmonary tuberculosis only was 374 per 100,000. Without a doubt there has been a marked decline in tuberculosis mortality in New York City, which is characteristic of most communities in this country at least, and indeed in most other sections of the civilized world as well. This decline has been going on for a long period of time, though in New York City, at least, it has experienced a rather marked acceleration during the last decade, and still continues, although with an apparent tendency for the curve of decline to flatten out.

The decline, which has characterized tuberculosis mortality for a long period of time, seems more recently also to be true for tuberculosis morbidity. For active new reported cases in New York City, for instance, the total number given for 1920 was 14,035, whereas by 1925, in

spite of increased facilities for uncovering the disease and increased knowledge on the part of the public with reference to it, the total number of new cases declined to 10,955.

That this has been true in many other communities is, of course, universally known. We have, for instance, in England and Wales, statistics covering a long period of time. In these countries, from 1851 to 1925, the death-rate per 100,000 for the pulmonary forms of the disease declined from 282 to 80, and for all forms of the disease from 357 to 104.

There is no question that tuberculosis mortality has been decreasing consistently for many years. It also seems certain that within more recent years the amount of active disease has decreased. How about tuberculous infection? Now we enter a realm fraught with considerable elements of doubt, where differences of opinion prevail. Bushnell states in his *Epidemiology of Tuberculosis* that we have accomplished apparently nothing in stopping the dissemination of the tubercle bacillus. On the other hand, there is considerable evidence to indicate that the extent of tuberculous infection from certain sources, and affecting certain age-groups at least, has been materially lessened, as we shall endeavor to point out later.

In analyzing these practically universal mortality declines, in studying the factors that may have been instrumental, and in appraising the methods recommended for attack and control, it is desirable to give a little consideration to this question of age-groups, and especially to the life periods in which tuberculosis is most conspicuous. Most students of the problem agree that there are three rather distinctive age periods for tuberculosis: the period of infancy and childhood; the young adult period from 15 to 30; and the middle-age period, centering about 45 to 50 years. These are the generally accepted significant age-groupings.

On the other hand, others have noted still further age-group divisions, reflected in the supposedly characteristic reactions of adult human beings, particularly to pulmonary tuberculosis. Brownlee in England assumes that he has demonstrated three clear-cut types of the disease in adult life. The first of these, the "young adult" type, measured against a statistical basis of mortality, shows a maximum death-rate in males between the ages of 20 and 25 years; the second, the "middle age" type exacts its maximum total between the ages of 40 and 45 years; while the third, the "old age" type, has its maximum mortality between the ages of 55 and 65 years. Brownlee is inclined to the belief that there exist two

distinct strains of tubercle bacilli which have a special age application. One of the strains attacks in early manhood and possibly also in old age, the other in childhood and middle life. This assumption is based upon exhaustive inquiries into the sociological, industrial, and other factors which might account for an unequal distribution in the prevalence of these alleged types of pulmonary tuberculosis. However, many bacteriological and other studies have thus far indicated that the tubercle bacilli, isolated from numerous cases of pulmonary tuberculosis, all conform to one well-defined serological type, and that any variations that exist are neligible. It would seem, therefore, that the theory which postulates two groups of human tubercle bacilli still remains to be proved, and that the present bacteriological evidence does not support this idea.

It will be more profitable to return to our previously mentioned classifications of childhood, young adult, and middle-age tuberculosis, especially if we are to attempt to reach even tentative conclusions as to why these widespread declines in tuberculosis mortality have been for many years, and are still taking place. You will realize at once, that it is not yet possible to assign relative values to the various influences that are undoubtedly at work. In a broad way, these influences might be classified somewhat as follows:

1. The Direct and Intentional Attack upon the Disease: This has involved measures aimed to limit infection, such as the pasteurization of milk and the isolation of positive cases; measures to limit disease, such as efforts at early detection and efforts to promote hygienic living and increased resistance to breakdown; and measures aimed to limit mortality, such as adequate hospitalization and treatment facilities. It is the speaker's belief that these influences have had a major effect in accelerating mortality decline in certain communities, especially during the past few years. There is plenty of evidence for this, although it must not be forgotten that the rates were declining before the modern campaign against tuberculosis had started, and that presumably, influences at work then are still at work now.

2. General Improvement in Social and Living Conditions, in Economic and Working Environments: Recent experience during the war and at other times has substantiated the logical assumption that tuberculosis, as an active disease and as a cause of death, has been and is materially affected by these considerations, as will be pointed out subsequently.

3. Possible changes in individual resistance and in group or race immunization, perhaps incidental to a gradual though universal tuberculization; possible

changes in the virulence of the organism and possible modifications in the race-stock composition of certain countries at least.

It is probable that these factors have been at work for a long time, though it is difficult, relatively or absolutely, to weight their importance. Yet some light may be thrown upon what has taken place by a recognition of the certainty that the greatest decline in tuberculosis mortality during the past few decades has taken place in childhood. In England and Wales, for instance, if one compares the mortality rates for 1851 with the average rate for the decade, 1901–1910, one finds that the percentage of improvement in the rate for males at all ages was approximately 50 per cent; for the middle-age-group of 45 to 50 the improvement was approximately 27 per cent; for the young-adult group of 20 to 24 the improvement was 62 per cent, and for the childhood group of 0 to 4 years, the improvement was approximately 75 per cent. It seems reasonable that we may assume with a fair degree of certainty that in childhood, at least, the volume of tuberculosis mortality is an approximate index as to the volume of infection. In infants and young children freshly infected with tuberculosis, the disease usually runs a rapid and frequently fatal course. Social and economic, and other environmental factors, are of relatively small importance. Consequently, if the death-rate in this age-group has fallen, and fallen to a greater degree than in any other age-group, it would seem to indicate that the amount of infection has been decreasing, and that opportunities, particularly for massive infection, have diminished. If the total number of active cases has decreased of late years, as indicated by the New York figures previously quoted, this source of childhood infection would necessarily have been reduced. All of the efforts to limit contacts with open positive-sputum cases, the efforts to find the disease in early stages, and the efforts through education and institutional provision to encourage a larger percentage of patients to follow satisfactory and safe methods of treatment,—all of these efforts presumably have lessened exposure for children. Then, too, as will be briefly discussed subsequently, there has been a marked decline in the volume of nonpulmonary tuberculosis among children, a form of disease which certainly to some extent followed infection with the bovine tubercle bacillus. This decline is, to a degree, a reflection of improved milk supplies, tuberculin-tested cattle, and especially of the extension of milk pasteurization. Much of the evidence at hand would seem to substantiate the assumption that the amount of tuberculous infection has de-

creased, and that this has been peculiarly reflected in the relatively great decline in tuberculosis mortality among infants and children.

What can be said concerning any special factors that may have effected the decline in the early adult group? Special educational efforts have no doubt supplemented the effects of the underlying changes in immunity that may have influenced tuberculosis as a cause of sickness and death in this age-group. Decreased infection may be a factor, although by no means of as great importance as is the case in childhood. In studying the problem and in endeavoring to "isolate" any special factors that may have been at work, Collis calls attention to the war experience and assumes that this period disclosed such a special influence. He points out that

> During this time, the mortality from pulmonary tuberculosis rose steadily from year to year in different countries in proportion as the food scarcity prevailed; but the rise was practically confined to early adult life, and was most pronounced in Britain, at any rate, in those areas where munition work called for undue output of energy; in childhood and late life (except in Central Europe where by 1918 food scarcity bordered upon a condition of famine) there was no rise for either sex in the phthisis mortality rates. Directly after the armistice, mortality fell as food became available, and the fall affected the ages at which the rise had occurred.

Collis believes that food supply in relation to energy output exerts a powerful influence upon tuberculosis mortality at this period of life. If this be true, then the marked declines that have been going on for many years in most countries in this age period reflect, in turn, the very general improvement in economic conditions, in food supplies, and in the food habits of the people generally.

There remains the so called middle-age or older age period to be considered. Here again Collis gives it as his opinion that infection is of slight if any importance, that food supplies are of relatively slight importance, and that a study of national records and particularly of industrial data "indicates that the attack upon males at this period of life is largely determined by the amount of wear and tear to which the human frame is exposed; that the mortality at these ages has fallen in all industrial countries as labor-saving devices have been introduced and as hours of labor have been curtailed." Pearl's independent conclusion supports this view, for he also believes that increasing physical demands upon energy have a detrimental influence upon mortality in general, including tuberculosis mortality, especially at ages over 45 years.

Not too much weight, of course, should be placed upon this distinction between the two adult age periods. Certainly the factors which seem preëminently to influence mortality in one period are by no means to be entirely ruled out as influences in the other period. On the other hand, this analysis by Collis and others would seem to indicate a fairly logical and substantiated division of factors, affecting not only the general decline in mortality at all ages, but to some extent specifically the decline at special ages. Any attempt further to assign relative values for such factors as industrial and occupational conditions, stress and strain, wear and tear, general economic conditions, food supplies, etc., or indeed to assign values to the more specific and conscious efforts at disease control by Health Departments, social agencies, physicians, and others, would be futile at this time. It is not only impossible to weight these factors relatively and comparatively with each other, but it is fundamentally out of the question to evaluate them individually or as a whole against the intangible but presumably important influences at work as a result of biological changes in the human organism, or in the tubercle bacillus itself. We can only appraise, in a general way, the aids that seem to have been instrumental in effecting the mortality decline and, in addition, we can, with some degree of rationality, estimate their probable effects upon certain broad age groups.

In the discussion above with reference to probable decrease in infection, reference was made to the problem of bovine tuberculosis, especially, of course, as it affects human tuberculosis in childhood. There seems to be no question that the control of milk supplies has been an important factor in limiting tuberculous disease in the younger age groups. As is well known, when the bacillus was first discovered by Koch, he believed that both the human and bovine bacilli were the same, and equally dangerous to either species. Koch later believed that the bovine bacillus infected cattle alone, and that the human bacillus infected human beings alone, and that cross infections were of no practical importance. It was later assumed that a child might be infected with the bovine bacillus, and that after a few years this microörganism might change its characteristics in adapting itself to the human being, and take on the features of the human bacillus. Subsequent investigations, particularly by Park in New York City, have indicated that if such changes ever do take place, they proceed very slowly and are of no practical significance. It was also clearly indicated that the bovine bacillus "causes serious progressive infections in little children, especially those under two years; that in older

children bovine infections were limited to glandular troubles, and that in adults, bovine infections became, as Koch had thought, of negligible importance."

Bacteriological, clinical, and autopsy findings subsequently indicated that for pulmonary tuberculosis in children under five years a little less than 3 per cent is of bovine origin; for tuberculous adenitis among children under five years 61 per cent was of bovine origin; for abdominal tuberculosis among children under five years, 47 per cent was of bovine origin. Small percentages were indicated for tuberculous meningitis, and for tuberculosis of the bones and joints. In summarizing the situation, Park from this investigation concluded that about 10 per cent of the tuberculosis of little children was due to bovine infections, and about 4 per cent of the mortality, and that this was affected in every country by the amount of raw milk consumed, and the amount of bovine infection among cattle. That the gradual development of tuberculin testing among cattle, and that the increased use of pasteurized milk have been instrumental in decreasing the amount of infection, disease and mortality from tuberculosis among children particularly, would seem to be substantiated by the figures for New York City, where pasteurization has gradually increased, and where it is now well-nigh universal. Evidence from the clinical side is not wanting. In New York City, in 1912 for instance, Park examined 50 lymph nodes taken from tuberculous children, and found that 20 of the children were infected with bovine tuberculosis. A later examination, in 1923, of a second group of 50 cases, indicated that only 6 were due to bovine infection, and that none of these 6 children had been fed on pasteurized milk. Between 1898 and 1923 the death-rate for tuberculosis among children under fifteen in New York City declined from 136 per 100,000 to 33 per 100,000. Park concludes, "In cities where pasteurization has been adopted, bovine infection has largely disappeared, while in countries such as England and Scotland, where pasteurization is less generally adopted, bovine infection is still a serious menace."

It seems therefore erroneous to conclude at this time that the amount of tuberculous infection is not decreasing. This, however, is not the only erroneous and antiquated conception still widely held with reference to tuberculous infection. It is, in fact, still quite widely assumed that tuberculous infection is extremely widespread, even in childhood. This may have been the case at one time, and may still be the case in some communities, especially in Europe, but it does not seem to be true for

American cities. Smith of New York has indicated that this belief is based largely on figures presented years ago by Hamburger and others for Vienna, a city in which tuberculosis is unusually prevalent. Smith points out that recent tuberculin studies of children in the larger municipalities in this country indicate that reports from most European cities show higher curves of infection, and that the application of European findings to American conditions is not a reliable procedure. The records for Vienna, for instance, indicated that by the time children are 13 years of age a little less than 95 per cent of them show positive tuberculin reactions; for Geneva a little less than 80 per cent; for Paris over 75 per cent. On the other hand, for St. Louis the figure is 48 per cent, for New York City 36 per cent, and for Philadelphia 32 per cent. Incidentally, it is notable that the American cities that show the lowest percentages of infection also are, for the most part, those communities where most effective control measures have been instituted, and where there have been the most marked declines in the number of deaths and the number of active cases of the disease. Fewer children show positive tuberculin reactions where the most has been done to promote pure milk supplies and to diminish the opportunities for contact with open cases of human tuberculosis.

These findings were to a degree substantiated by a tuberculin survey carried out in Framingham, Massachusetts, in conjunction with the Health and Tuberculosis Demonstration there during the period, 1917–1923, inclusive. This Pirquet tuberculin survey took place during June, July, and August of 1917, covering a group of 460 children between the ages of one and seven years. In summarizing the conclusions of this study, it may be said that about 33 per cent showed positive reactions, although the percentage of positives in the age-group 6 to 7 years was 54. In this study an effort was made also to classify the findings according to race-stock, and it is believed that the results obtained in Framingham may indicate that this is an important consideration, although the total number of cases, when distributed according to race groups, is broken up into such small groups as to make conclusions from a statistical point of view of little more than indicative value. However, it is interesting to note that the percentage of positives among children in Italian families was 51, which was in marked contrast to the percentage of positives found among children of Irish parentage, where the figure was only 30 per cent. In contrast to this, the number of active adult cases found among the Italians in the population was strikingly low, whereas the

number of active cases in the Irish stock generally was high. This corresponds to a low tuberculosis mortality rate among Italians, and a uniformly high one among Irish groups. At the time this was considered rather difficult of interpretation, though it was assumed that it possibly indicated that the tuberculin reaction measures the resistance to infection, in which case, assuming a fundamental difference in general race-stock resistance to the disease, with a greater exposure and a more widespread infection among Irish children one might find a milder and less frequent tuberculin reaction than would be the case in a more resistant stock.

The tabulation of these tuberculin cases in Framingham according to districts of the community was also interesting. There was one section of the city known as Coburnville inhabited almost entirely by Italians, where the percentage of positive reactions was 46. Saxonville, an Irish community, on the other hand showed a percentage of positive reactions of 23. Hygienic conditions in each section were equally poor, and the contrast seemed to be explained largely on a basis of the distinction in race groups. This finding in turn suggested a possible interpretation of the tuberculin reaction as a measure of resistance or immunity. Another interesting conclusion of this Framingham study was that a thorough medical examination of all the children, negative and positive, disclosed not a single case on a basis of history and physical examination that could be called actively tuberculous. Further than that, a subsequent follow-up during a period of years brought forth not a single case of active tuberculosis among those children who had shown a positive tuberculin reaction.

There is one other tuberculin survey with which the speaker is familiar that definitely corroborates these Framingham findings and the interpretations given to them. We refer to a study made by Distaso and Johnson in Wales, reported in *Tubercle* for January, 1922. We cannot cite the detailed observations, but we should like to quote certain conclusions from this study as follows:

> If we think over the resistance to infection shown by this group, we find . . . . that there are no cases of open tuberculosis present, and that the parents who have a positive Von Pirquet reaction do not show any signs of disease. In these families the disease is no longer infective and the reaction only signifies that immunity has been acquired. The Von Pirquet reaction, therefore, is a reaction of immunity under whatever conditions it may arise.

These writers also draw certain general conclusions with reference to the epidemiology of tuberculosis, especially pulmonary tuberculosis. They point out that immunity arises in nature, as a result of a gradual, minimum, continuous infection and tuberculization.

> In order that immunity shall arise, the contact must take place at intervals, only small quantities of the virus being absorbed. Under these circumstances, the human organism mobilizes its defenses and can cope with the infection. . . . . People in intermittent contact with open cases get only a Von Pirquet positive, but not the active disease, deriving benefit, not harm from the small doses of bacilli to which they are exposed. On the other hand, the facts brought out through this inquiry show that when the virus is absorbed continually (or massively) as in the intimate contact of mother and child, then active tuberculosis arises.

For the most extensive and authoritative comments upon the epidemiology of tuberculosis, I must refer you to the book previously mentioned, issued in 1920 by Colonel George E. Bushnell. Except for his assumption that infection has not been decreased, you will find that his general conclusions coincide with the interpretations given in the foregoing to the many studies and references cited. Bushnell shows clearly the marked contrast between universal tuberculization and freedom from contact with the disease. He says:

> In studying the dissemination of tuberculosis throughout the world, it appears that, as respects the types of tuberculosis, the various countries are divided into two classes. In the one, tuberculosis is widespread, as with us; in the other it is relatively rare, but the cases that do occur are rapidly fatal, although under conditions favorable for it the disease may prevail as an epidemic and exterminate entire families and even tribes. This observation is formulated in the law of Römer, which is: Where tuberculosis is a rare disease the cases that occur will be acute and fatal. Where the disease is common the type will be chronic and relatively benign. In other words, contact with tuberculosis affords a certain protection against it.

But, of course, it is essential to keep that contact to a minimum. Under modern civilized conditions, general tuberculization is inevitable and presumably desirable. Anything that we can do to cut off major sources of infection will but eliminate the overwhelming dose, and will not interfere with the ubiquitous immunizing contacts. Infections with

the bovine bacillus may well be eliminated. Massive infections between mother and child serve only an evil purpose. To quote Bushnell again:

> Modern civilization brings with it inevitably a tuberculization. There appears to be no escape from this without more radical changes in our mode of life than can be reasonably anticipated. . . . . There is, however, no reason for alarm in the fact that the modern world is a tuberculous world. The present situation doubtless leaves much to be desired, but it is to be remembered that it has greatly improved within the last fifty years. . . . . We have simply to follow the indications that Nature grants us and resolve that the already large percentage of the immune shall be increased to one hundred per cent. Better care of the infant and the inauguration of an intelligent instruction of the mothers is the best way in which so happy a state can be approximated. The study of the tuberculosis of the Orient leads to the suspicion that good hygiene, however important and highly to be desired it may be, is of distinctly minor importance in comparison with an optimal tuberculization.

Then Bushnell concludes that in view of the terribly wasteful results in human life following Nature's methods of tuberculization, it is to be most earnestly hoped that the natural procedure shall be replaced by a thoroughly scientific method of artificial inoculation in which no life will need to be sacrificed.

And while we cannot fully discuss it here, it is possible to-day to hold out more hope for the accomplishment of this objective than was the case in 1920. The work of Calmette and Guérin on calves and monkeys and more recently on newborn infants, involving vaccination against tuberculosis with a living attenuated tubercle bacillus, has convinced these and other investigators that the procedure is harmless, and at the same time highly effective. Recently the records for 423 infants for the first six months after vaccination have been issued, with decidedly encouraging results. This group included a large number definitely exposed within the family. Further records are shortly to be published. More work must be done along this line before definite conclusions can be reached. Investigations are under way at many points both in Europe and in this country to attempt to analyze and corroborate the findings of Calmette. Whether Calmette's procedure with an attenuated microorganism is going to prove effective only further and more prolonged experiment can indicate. Whether a successful vaccination procedure must involve the use of virulent tubercle bacilli on the assumption that

no tuberculosis immunity is established without the development of an actual lesion showing incidentally a positive tuberculin reaction, as held by some critics of Calmette's work, still also remains to be substantiated. However, our investigators seem at last to be following decidedly promising trails, and scientific interest is being directed toward these attempts to control by artificial means one of the most serious affections of the human race. It is certainly not too much to hope that Bushnell's final aspiration may ultimately be realized.

What then, in the light of these epidemiological observations constitutes a legitimate and practical tuberculosis programme. We must certainly limit excessive infection either from human or bovine sources, and especially for children. We can certainly supplement the partial and inevitable immunity through generalized tuberculization by increasing individual resistance, presumably not to infection, but at any rate to disease and breakdown, through the promotion of personal hygiene. Improvements in general economic conditions, food supplies, occupational adjustments, and the control of mental and physical stress and strain will undoubtedly contribute much to the conquest of the disease. In the development of practical machinery for handling the disease, the perfection of devices to find active tuberculosis in an early stage is essential. In many communities the next step in bringing active tuberculosis under control is the first practical administrative step, long neglected, namely, the discovery of active cases in the early stages. This is being done by encouraging reporting, by the development of clinic service, by the provision of expert medical consultation service for diagnosis and advice with reference to treatment. Of course, in rounding out community machinery, this must be supplemented by adequate home and institutional facilities for the early and prolonged care of active cases and for the education of patients and the public in general concerning the essentials of tuberculosis therapy. Obviously, a full knowledge of the application of these essentials on the part of the medical profession is vital.

While there is much still to learn about tuberculosis, there never was a time when we knew so much about the disease. While our knowledge is still fragmentary, it is no longer haphazard. We begin to see the framework, and the obvious gaps can be identified. The situation was never so promising.

The coöperation of all interested and concerned is essential. Further research along immunological lines in the field of bacteriology and serology occupies indeed a hopeful position. This work in tuberculosis should go forward with the other striking current developments in immunology. We have practised vaccination against smallpox on an empirical basis for generations. We have an assured procedure against typhoid fever. More recently diphtheria and scarlet fever, and now perhaps measles, are being brought within the range of specific prophylatic control. What a conquest for immunology if tuberculosis can soon be added to this string of victories!

As the situation stands at present, however, adequate measures to limit the spread of infection and competent machinery to find and care for active tuberculosis cannot be neglected. Popular health education, with special emphasis upon periodic health examinations and upon the fundamentals of personal hygiene is vital. And it is especially important to realize that whatever the research findings, and however adequate the therapeutic provisions and the health educational measures, the chief obligation for the application of these findings, and for the effective use of existing knowledge as well as for the ultimate conquest of the disease, must inevitably rest upon the practising physician.

For the concrete interpretation of the products of research, for the effective and timely use of therapeutic facilities, and for the establishment of a practical service basis underlying our health educational superstructure, we must continue to look to the practical laboratory investigator with his test-tubes and microscopes, and then to the physician or clinic chief with his diagnostic eye, hypodermic needle, and persuasive, guiding, individual influence exerted upon the sick and the well. Through the practical interpretation of scientific data by the physician, through his increased contact with the underpar individual, or indeed with the well individual in health examination or similar work, through his more ambitious entering into the new and great field of the private practice of preventive medicine—through these contacts and developments are we led, perhaps peculiarly in the tuberculosis field, to justify a growing hope for the control of the ever-widening range of so called preventable causes of unnecessary illness and premature death. Essential to the conquest of tuberculosis is a rational, balanced interworking of the expert scientific investigator, the popular health educator, the clinic and sanatorium director, and the intelligent practitioner of medicine.

NOTES REGARDING TUBERCULOUS INFECTION IN NORTHEASTERN MINNESOTA

A. T. LAIRD, L. G. GUYER AND W. BAILEY[1]

The prevalence of active tuberculosis varies greatly in different localities. This is evident from the fact that the death-rate from the disease among whites in the United States in 1923 was 139 per 100,000 in Tennessee and only 16 in Utah (1).

There are equally great variations in the amount of latent infection indicated by tuberculin tests. Drolet (2) reports 65 per cent of positive cutaneous reactions among children in New York City, and Slater (3) 10 per cent among children in rural Minnesota. Ferguson (4) reports 40 per cent positive reactions (intracutaneous test) among children in Saskatchewan, and White (5) 8 per cent among white children in St. Louis, Missouri (Pirquet tests). Hamburger (6) found over 94 per cent of positive cutaneous reactions (Pirquet test) among adults in Austria (Vienna), and Calmette (7) 88 per cent in France (Lille), while Powell (8) reports only 5 per cent among native recruits in India.

There are similar but less marked variations in the amount of tuberculosis found postmortem. Naegeli (9) found evidence of tuberculous infection in 71 per cent of 500 autopsies in Zürich reported in 1900, while Adami and McCrae (10) found such evidence in only 41.7 per cent of 1,000 autopsies in Canada reported in 1908. Robertson (11) reports demonstrable lesions of tuberculosis, aside from pleural adhesions, in 67.5 per cent of 1,000 autopsies at the Mayo Clinic in 1922, but in only 43.6 per cent of 250 autopsies in Minneapolis in 1908–1910, and in only 16.8 per cent of 250 autopsies by Bell of Minneapolis in 1923–1924.

Among factors affecting the prevalence of tuberculosis, the character of the population, the racial strains composing it, the presence of descendants of tuberculous parents, density of population, standards of living, the opportunities for infection from human and bovine sources, are all of special interest. The methods used to secure evidence regarding these matters also deserve consideration.

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In this paper we are considering especially the influence of nationality, tuberculous ancestry and exposure to infection. Data regarding these factors have been tabulated by members of the Nopeming Sanatorium staff from records of the institution and of tuberculosis clinics conducted as part of its fieldwork. These cases are grouped as follows:

(1) Clinical cases of tuberculosis.

(2) Cases not presenting definite evidence of clinical tuberculosis (not clinically tuberculous).

(3) Cases not clinically tuberculous but presenting evidence of latent infection (positive Pirquet).

(4) Cases without evidence of either clinical tuberculosis or latent infection (presumably not infected).

The data are assembled in the following tables 1 to 21.

TABLE 1

Clinical cases of tuberculosis

Nationality of 587 positive-sputum cases at the sanatorium compared with the population of Duluth (nationality) and of St. Louis County (nativity)

NATIONALITY	TUBERCULOUS PATIENTS		POPULATION OF DULUTH	ST. LOUIS COUNTY
	number	*per cent*	*nationality percentage*	*nativity percentage*
Finnish	189	32.2	5.4	8.4
Swedish	89	15.2	16.2	5.9
Norwegian	75	12.8	11.1	3.5
American	67	11.4	24.2	54.9
Austro-Hungarian	45	7.7	2.6	0.8
Canadian	32	5.4	11.2	3.3
Polish	16	2.7	4.1	
Miscellaneous	74	12.6	25.2	23.2
	587	100.0	100.0	100.0

TABLE 2

Clinical cases of tuberculosis

Number of natives of various foreign countries under each classification of the National Tuberculosis Association "on admission" and "on discharge" in a series of 847 positive-sputum cases

NATIVITY	CONDITION ON ADMISSION											CONDITION ON DISCHARGE						
	Suspect	Minimal			Moderately advanced			Far advanced			Total	Arrested	Apparently arrested	Quiescent	Improved	Unimproved	Died	Total
		A	B	C	A	B	C	A	B	C								
Austria		1		1	7	11	8	4	5	22	59	2		1	4	1	51	59
Bohemia										1	1						1	1
Bulgaria							1			2	3						3	3
Canada					2	3	1	1	3	18	28	1		2		2	23	28
Croatia				1	1		1		1	5	9						9	9
Denmark										2	2						2	2
England									1	3	4						4	4
Finland		6		4	8	13	23	8	13	111	186		2	4	10	1	169	186
Germany							1			4	5						5	5
Greece							1			3	4						4	4
Hungary							1	1		1	3				1		2	3
Ireland								1		1	2						2	2
Italy			1		2	1	2	1		2	9	1					8	9
Jugo Slavia					1	1	1			6	9				1		8	9
Lithuania										1	1						1	1
Montenegro										2	2						2	2
Norway		2	2	2	7	4	7	1	6	31	62	1	2	2	3		54	62
Poland		1				2	3			5	11	1		1			9	11
Russia					3					3	6	1		1	1		3	6
Scotland		1			1						2				2			2
Serbia										3	3						3	3
Slavania										1	1						1	1
Sweden		4	1		4	7	10	4	11	49	90		3	1	11		75	90
United States	2	13	3	4	24	17	35	13	28	203	342	6	5	9	30	8	284	342
No data								1		2	3					1	2	3
Total	2	28	7	12	60	59	95	35	68	481	847	13	12	21	63	13	725	847

TABLE 3

Clinical cases of tuberculosis

Percentages of various conditions "on admission" and "on discharge" in foreign-born patients in a series of 847 positive-sputum cases (see table 2)

CONDITION	FINLAND	SWEDEN	NORWAY	UNITED STATES
Suspect				0.6
Minimal A	3.2	4.4	3.2	3.8
Minimal B		1.2	3.2	0.9
Minimal C	2.1		3.2	1.2
Moderately advanced A	4.3	4.4	11.3	7.0
Moderately advanced B	7.0	7.8	6.5	5.0
Moderately advanced C	12.4	11.2	11.3	10.2
Far advanced A	4.3	4.4	1.6	3.8
Far advanced B	7.0	12.2	9.7	8.2
Far advanced C	59.7	54.4	50.0	59.3
Total	100.0	100.0	100.0	100.0
Quiescent	2.1	1.1	3.2	2.6
Apparently arrested	1.1	3.3	3.2	1.5
Arrested			1.6	1.8
Improved	5.4	12.5	4.8	8.8
Unimproved	0.5			2.3
Died	90.9	83.1	87.2	83.0
	100.0	100.0	100.0	100.0

TABLE 4

Clinical cases of tuberculosis

Ratios of natives of certain foreign countries to the total number of patients under each classification of the National Tuberculosis Association in a series of 847 positive-sputum cases (see table 2)

	FINLAND	SWEDEN	NORWAY	UNITED STATES	MISCELLANEOUS	TOTAL
Minimal A	21.4	14.3	7.1	46.4	10.8	100
Minimal B		14.3	28.6	42.9	14.2	100
Minimal C	33.3		16.7	33.3	16.7	100
Moderately advanced A	13.3	6.7	11.7	40.0	28.3	100
Moderately advanced B	22.0	11.9	6.8	28.8	30.5	100
Moderately advanced C	24.0	10.5	7.3	36.8	21.4	100
Far advanced A	22.9	11.3	2.9	37.1	25.8	100
Far advanced B	19.1	16.2	8.8	41.2	14.7	100
Far advanced C	23.1	10.2	6.4	42.2	18.1	100
Quiescent	19.0	4.8	9.5	42.9	23.8	100
Apparently arrested	16.7	25.0	16.6	41.7		100
Arrested			7.7	46.2	46.2	100
Improved	15.9	17.5	4.8	47.6	14.3	100
Unimproved	7.7			61.5	30.8	100
Died	23.3	10.3	7.4	39.3	19.7	100

TABLE 5

Clinical cases of tuberculosis

Tuberculous ancestry in 1,115 tuberculous cases at the Sanatorium

PATIENTS WITH HISTORY OF TUBERCULOSIS IN PRECEDING GENERATION		PATIENTS WITHOUT HISTORY OF TUBERCULOSIS IN PRECEDING GENERATION	
number	*per cent*	*number*	*per cent*
157	14.1	958	85.9

TABLE 6

Clinical cases of tuberculosis

Tuberculous ancestry among various nationalities (foreign-born or born of foreign-born parents both of the same country) in a series of 587 positive-sputum cases at the sanatorium

	TUBERCULOSIS IN PRECEDING GENERATION	TOTAL PATIENTS OF NATIONALITY CONCERNED	PERCENTAGE
Finnish	16	187	8.6
Norwegian	6	75	8.0
Swedish	13	89	14.6
Canadian	4	30	13.3
Polish	3	16	18.7
Austro-Hungarian	2	45	4.4
Jugo-Slavic	1	9	11.1
Miscellaneous	0	136	0.0
	45	587	7.7

TABLE 7

Clinical cases of tuberculosis

Exposure to infection among 1,115 tuberculous cases at the Sanatorium

	NUMBER	PER CENT
Preceding generation	157	14.1
Immediate generation	109	9.8
Succeeding generation	4	0.4
Consorts	25	2.2
Other sources	78	7.0
Unknown (but inquiry made)	742	66.5
	1115	100.0

TABLE 8

Clinical cases of tuberculosis

Exposure to infection in a series of 847 positive sputum cases at the Sanatorium

	PER CENT
Preceding generation	9.9
Other sources	18.9
Unknown	71.2
Total	100.0

TABLE 9

Cases not clinically tuberculous

Distribution of nationalities in a series of 2,387 cases not clinically tuberculous

NATIONALITY	DULUTH CLINIC		RANGE TOWN CLINICS		RURAL CLINICS		TOTAL	
	number	*per cent*	*number*	*per cent*	*number*	*per cent*	*number*	*per cent*
United States	312	24.0	122	12.8	6	4.5	440	18.4
Finnish	274	21.1	400	41.9	114†	86.4	788	33.0
Swedish	153	11.8	65	6.8	8	6.1	226	9.5
Norwegian	122	9.4	50	5.2	2	1.5	174	7.3
Austrian	*		136	14.3	1	0.8	137	5.7
Italian	34	2.6	42	4.4			76	3.2
Russian	52	4.0	*				52	2.2
Polish	51	3.9	*				51	2.1
German	31	2.4	15	1.6			46	1.9
British	36	2.7	36	3.8			72	3.0
Canadian	*		21	2.2			21	0.9
Slavic	6	0.5	27	2.8			33	1.4
Others	230	17.7	40	4.2	1	0.8	271	11.3
Total	1301	100.0	954	100.0	132	100.0	2387	100.0

* So few that they were included in *miscellaneous*.

† Also at a series of clinics held in school-houses; total attendance of 520 was practically all Finnish.

TABLE 10

Cases not clinically tuberculous

Tuberculous ancestry in a series of 3,301 cases not clinically tuberculous

	DULUTH CLINICS		RANGE TOWN CLINICS		RURAL CLINICS		TOTAL	
	number	*per cent*	*number*	*per cent*	*number*	*per cent*	*number*	*per cent*
Tuberculous history in preceding generation	431	24.6	218	24.1	55	8.6	704	21.3
No record of tuberculosis in preceding generation	1,322	75.4	687	75.9	588	91.4	2,597	78.7

TABLE 11

Cases not clinically tuberculous

Exposure to infection in a series of 3,301 cases not clinically tuberculous

	DULUTH CLINICS		RANGE TOWN CLINICS		RURAL CLINICS		TOTAL	
	number	*per cent*	*number*	*per cent*	*number*	*per cent*	*number*	*per cent*
Exposure in preceding generation	431	24.6	218	24.1	55	8.6	704	21.3
Other exposure	278	15.8	132	14.6	58	9.0	468	14.2
No record of exposure	1,044	59.6	555	61.3	530	82.4	2,129	64.5

TABLE 12

Cases not clinically tuberculous presenting evidence of latent infection (positive Pirquet)

Distribution of nationalities in a series of cases not clinically tuberculous but reacting positively to the Pirquet test

NATIONALITY	NUMBER TESTED	NUMBER POSITIVE	PER CENT POSITIVE	PERCENTAGE OF TOTAL 202 POSITIVE
United States	222	50	22.5	24.8
Finnish	115	37	32.2	18.3
Swedish	76	24	31.6	11.9
Norwegian	70	17	24.3	8.4
Italian	20	8	40.0	4.0
Russian	33	4	12.1	2.0
Polish	36	9	25.0	4.4
German	19	5	26.3	2.5
British	16	3	18.8	1.5
Others	142	45	31.0	22.3
Total	753	202	26.8	100.0

TABLE 13

Tuberculous ancestry in a series of cases not clinically tuberculous but reacting positively to the Pirquet test

	NUMBER	PER CENT
Tuberculous history in preceding generation	90	37.0
No record of tuberculosis in preceding generation	153	63.0
Total	243	100.0

TABLE 14

Exposure to infection in a series of cases not clinically tuberculous but reacting positively to the Pirquet test

	NUMBER	PER CENT
Exposure in preceding generation	90	37.0
Other exposure	45	18.5
No record of exposure	108	44.4
Total	243	100.0

TABLE 15

Distribution of nationalities in a series of 551 cases not clinically tuberculous and not reacting positively to the Pirquet test

NATIONALITY	NUMBER	PER CENT
United States	172	31.2
Finnish	78	14.2
Swedish	52	9.4
Norwegian	53	9.6
Italian	12	2.2
Russian	29	5.3
Polish	27	4.9
German	14	2.5
British	13	2.4
Slavic	3	0.5
Others	98	17.8
Total	551	100.0

TABLE 16

Tuberculous ancestry in a series of 667 cases not clinically tuberculous and not reacting positively to the Pirquet Test

	NUMBER	PER CENT
Tuberculous history in preceding generation	177	26.5
No record of tuberculosis in preceding generation	490	73.5
Total	667	100.0

TABLE 17

Exposure to infection in a series of 667 cases not clinically tuberculous and not reacting positively to the Pirquet test

	NUMBER	PER CENT
Exposure in preceding generation	177	26.5
Other exposure	108	16.2
No record of exposure	382	57.3
Total	667	100.0

TABLE 18*

Clinically nontuberculous employees

BIRTHPLACE	EMPLOYEES	PARENTS
United States	71	18
Finland	4	23
Norway	2	7
Sweden	1	15
Austro-Hungarian	4	8
Miscellaneous	8	19
	90	90

* Corrected April 9, 1926.

TABLE 19

Clinically nontuberculous employees

TUBERCULOUS ANCESTRY	NUMBER	PER CENT
History of tuberculosis in parents or near relatives	27	32.9
No such history	55	67.1
Total	82	100.0

TABLE 20

Clinically nontuberculous employees

	NUMBER	PER CENT
Exposure to infection:		
History of exposure to infection	40	47.6
No history of exposure	44	52.4
Total	84	100.0

TABLE 21

Clinically nontuberculous employees

	NUMBER	PER CENT
Pirquet reactions:		
Positive Pirquet reaction	35	39.3
Negative Pirquet reaction	54	60.7
Total	89	100.0
X-ray examinations:		
Evidences of latent tuberculosis	29	34.0
No evidence of latent tuberculosis	57	66.0
Total	86	100.0

COMMENT

Something over half (55 per cent) of the population of St. Louis County, Minnesota, (206,000) is foreign born. In its largest city (Duluth) about three-quarters of the population is of foreign stock, that is, consisting of children of the foreign-born parents. The principal nationalities represented are the Finnish, Swedish and Norwegian. In the city the Swedish and Norwegian outnumber the Finns, but in the country many districts are settled exclusively by Finns.

Of 587 positive-sputum cases at the Sanatorium 32 per cent were Finns and 28 per cent Swedish or Norwegian. Foreign-born patients of these nationalities reached the far-advanced stage before admission in about the same proportion as American patients; a somewhat larger percentage of the Finns (91) and the Norwegians (87) died than of the Swedes and the Americans (83). The average duration of the disease was 22 months for the Finns (189 cases); 28 months for the Swedes (90 cases); 41 months for the Norwegians (62 cases); and 25 months for the Americans (342 cases) in a group of positive-sputum cases (847 cases).

As regards tuberculosis in the preceding generation, 14 per cent of over 1,000 tuberculosis patients (1,115) at the Sanatorium gave such a history, but only 8 per cent of a positive-sputum group (587 cases). Twenty-one per cent, however, of persons not clinically tuberculous (3,301 cases) reported tuberculosis in the preceding generation.

Exposure to infection was reported in 34 per cent of sanatorium patients (1,115 cases), but in only 29 per cent of a series of positive-sputum cases (587). A history of exposure was, however, obtained in 36 per cent of the nontuberculous group.

It will be observed that our percentage of positive Pirquet tests among adults is lower than is generally reported from eastern or European communities, 26.8 per cent among 753 cases not clinically tuberculous.

Our tables on the whole confirm Drolet's claims (2) that a history of parental tuberculosis is as common among persons who show no evidence of tuberculosis as it is among those who have definite clinical disease. Exposure to tuberculous infection is reported fully as often by those who are apparently well as by sanatorium cases. However, both history of ancestral tuberculosis and the occurrence of exposure to infection from human sources seem to be very much less common in the rural districts of Minnesota than in New York City. Drolet reports exposure to infection in 85 per cent of 871 children in New York, while our nurses could obtain such a history for only 8 per cent of 394 Finnish children examined by us in rural schools in Minnesota.

Lampson (12) has made some interesting studies, in which the rôle of exposure to known open cases of tuberculosis is especially considered. The open cases were designated as *centre cases*, and the persons exposed to infection by them were examined thoroughly. Histories were taken, and physical examinations and tuberculin tests were made and recorded.

In Lampson's first study, 33 tuberculous families in which there were cases with positive sputum are considered; 173 individuals in these families were examined. Excluding the centre cases 67 per cent showed evidence of infection with the tubercle bacillus. In 15 nontuberculous families 80 individuals were examined, of whom only about two ($2\frac{1}{2}$) per cent showed evidence of infection.

In the second series Lampson (13) studied 97 family groups. Charts were made for 449 individuals; 79 per cent of the individuals fully exposed for a long period of time to cases with positive sputum became infected. A much smaller percentage, 28 per cent of those partially exposed or exposed for a short period of time, were infected. Only a small percentage, 8 per cent, of those without a definite history of exposure showed any evidence of infection. Positive Pirquet reactions were obtained in 70 per cent of 384 individuals exposed to open cases of pulmonary tuberculosis, in 32 per cent of 34 individuals exposed to nonpulmonary tuberculosis and in only 10 per cent of 31 individuals without history of exposure.

A certain number of negative Pirquet reactions may be charged to the personal equation, to variation in methods of performing and reading the tests. An additional number may be accounted for by the temporary

presence of anergic states in infected persons. Austrian (14) reports that at the Johns Hopkins Dispensary one lad gave a positive Pirquet reaction in 1915, a negative reaction in 1920, a positive in 1921 and again a negative in 1923. Making due allowance for all such sources of error, there seems to be in Minnesota a larger proportion of uninfected and presumably unprotected adults than in Eastern cities. Theoretically, this would mean that when exposed to infection such individuals ought to be practically virgin soil for tuberculosis. Many cases of the primary type of the disease unmodified by previous infection should be seen, large numbers should succumb promptly to slight exposure, and, in short, conditions should be similar to those found among nontuberculized people in the South Sea Islands. Practically, this does not seem to be the situation. If it were, the employment of the sons and daughters of Finnish farmers at the Sanatorium would be fraught with special danger. In our series of over 1,000 presumably nontuberculous employees, there have developed 10 cases of definite clinical tuberculosis, 5 of which have had positive sputum and 3 of which have died. It is possible that among untraced discharged employees other cases may have developed. The total, however, is not more than the morbidity elsewhere in the community, and the development of some of the cases may be attributed to known exposure before there was any connection with the institution. Toan (15) reports 4 cases developing among 857 employees not presenting clinical evidence of tuberculosis at the Michigan State Sanatorium.

In conclusion, it is probable that our neighbors from northern Europe, while relatively susceptible to tuberculosis, possess a degree of inherited immunity, not recognizable by tuberculin tests which modifies the course of the disease.

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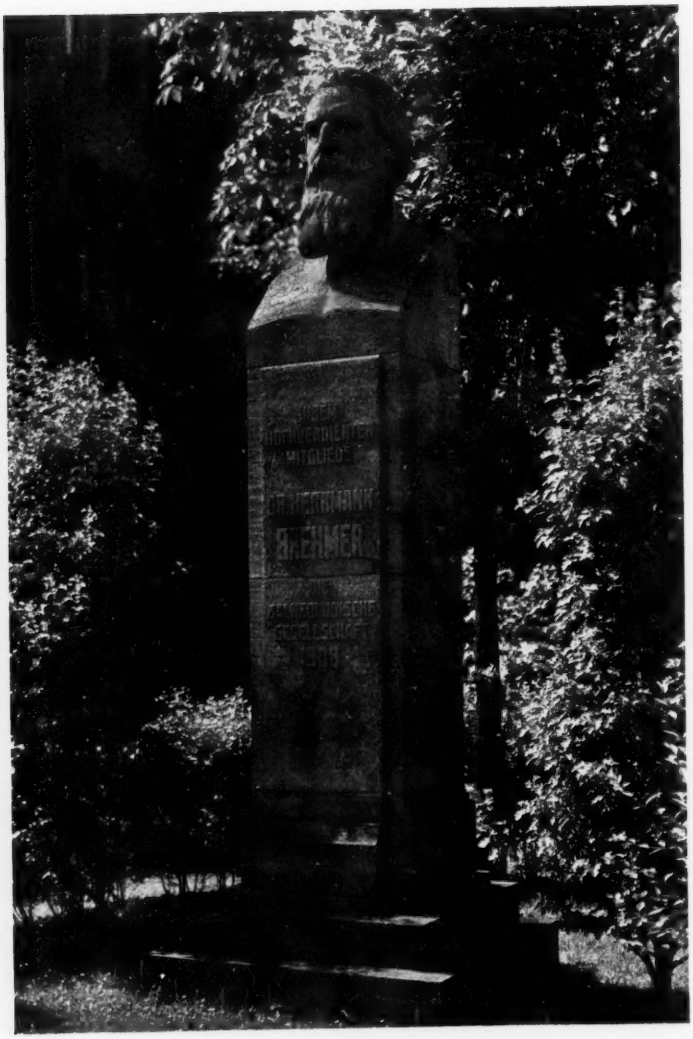

BREHMER MONUMENT AT BRESLAU

THE CENTENARY OF BREHMER'S BIRTH

S. ADOLPHUS KNOPF

The great pioneer of modern sanatorium treatment, Hermann Brehmer, who has given the inspiration to hundreds, if not thousands, of men to establish sanatoria for the treatment of the tuberculous, was born August 4, 1826. This date will be celebrated throughout Germany; and, since our great Trudeau and many others in this country may also be called Brehmer's disciples, it may perhaps be well to recall the man's achievements in our AMERICAN REVIEW OF TUBERCULOSIS.

Hermann Brehmer, born in Kurtsch, Province of Silesia, Prussia, attended the Elisabeth Gymnasium in Breslau, and after receiving his classical degree went to the universities of Breslau and Berlin, studying natural philosophy and mathematics. Johannes Müller, the great physiologist, was at that time lecturing in Berlin, and Brehmer was so attracted by these lectures that he decided to study medicine instead of mathematics. After finally graduating in medicine he began to practise in the little village of Goerbersdorf, which at that time had no more than 900 inhabitants.

It was already his intention to establish an institution for the exclusive treatment of consumptives. His thesis for the final degree is characteristic of his conviction and optimism concerning the curability of tuberculosis in the earlier stages of the disease. It was published in 1853, and its title was *De legibus ad initium atque progressum tuberculosis pulmonum spectantibus*.

The Prussian Government at that time did not encourage Brehmer's scheme to establish a sanatorium for consumptives, and he could not get the official authorization to open his *Heilanstalt*. It is hardly possible that this was due to an official phthisiophobia, but I am inclined to believe that his very democratic ideas, which were not favorably looked upon by the Prussian Government, were the real hindrance to the carrying out of his beautiful project. Fortunately for Brehmer, he had two powerful friends in Humboldt and Schoenlein. Thanks to their intervention, he finally received the concession to build his sanatorium. It had naturally a small beginning, but the success of the institution was

marvellous. In 1862 he was able to enlarge the institution considerably, and to-day it is still one of the largest private institutions of its kind in the world. It has now a division for the well-to-do, one for the middle classes, and one for the poor, and can accommodate about 300 patients.

While Brehmer's conception of the aetiology of consumption and his views on therapeutics and climatology have been somewhat modified by his pupils and followers, among whom we must mention as the most distinguished, Peter Dettweiler, it is nevertheless of great historical interest to know just what Brehmer thought of the causes and treatment of tuberculosis. In his pathological studies he had observed the fact that in the great majority of the bodies of consumptives which came to autopsy there was an abnormal proportion between the size of the heart and that of the lungs. He found the lungs large, while the heart was unusually small, with thin, relaxed, and weak muscular walls. Nobody, up to this time, had thought of considering these abnormal proportions of the thoracic viscera as of any aetiological importance; Brehmer reasoned that the small and weak heart ultimately led to a diminished circulation and a subsequently disturbed nutrition of pulmonary tissue. As a consequence of his logic he recommended high altitudes as a factor in the treatment of tuberculosis, since a diminished atmospheric pressure demands an increase of heart action and a subsequent increase of metabolism. He ascribed the relative freedom from phthisis among the people living in mountainous districts to this condition of higher pulse-rate and stronger heart. His studies of the geographical distribution of the disease seemed to confirm his conclusions in this respect. He studied, however, also the mode of life of certain classes of people relatively free from phthisis in lowlands, and learned that an increased bodily exercise, under proper hygienic and dietetic conditions, was also a reason for relative freedom from phthisis among certain people, though they might live in ordinary altitudes. Brehmer's therapy was, therefore, to treat his patients in an altitude in which he thought mankind would be immune from phthisis because of diminished atmospheric pressure and its result on the thoracic viscera; and, second, to supply his patients with rich food, particularly milk, and also some alcohol, combined with physical exercise, under constant medical supervision,—all with the same point in view, that is, to strengthen the heart, improve pulmonary and general circulation and nutrition, and bring about an increased metabolism.

We know that Brehmer's theory of the immune zones in high altitudes cannot be absolutely accepted. We have also learned from his cele-

brated pupil, Peter Dettweiler, that the rest-cure is fully as important in pulmonary tuberculosis as is judicious exercise. Furthermore, the experiences of the past years have shown that sanatorium treatment at sea level, in a pure atmosphere, can be carried out as successfully as in higher altitudes. But all this does not detract from the value of Brehmer's work, nor does it diminish the gratitude which the medical profession and humanity at large owe him. He was the founder of the first sanatorium for consumptives, and he has restored thousands to health who, under ordinary treatment in vogue at that time, would certainly have fallen victims to the disease.

The hygiene practised by Brehmer in his sanatorium, particularly that portion appertaining to the prevention of tuberculosis, bore unusual fruits. It demonstrated for the first time that in a sanatorium for consumptives, properly equipped and properly managed, one was safer from contracting tuberculosis than anywhere else. It demonstrated further (and this is a lesson which our phthisiophobiacs may well take note of) that a sanatorium under proper medical supervision was not a danger to the neighborhood, but a blessing.

It is interesting to note here that as the result of Brehmer's activities in Goerbersdorf the mortality from tuberculosis among the villagers was reduced within a few years to one-third of what it was before the establishment of Brehmer's sanatorium. The reduction in the mortality from tuberculosis among the villagers must be ascribed to the conscious and unconscious imitation of the cleanly habits which the inmates of the sanatoria are obliged to practise. But the presence of the sanatoria in Goerbersdorf has not only been a blessing to the village in a sanitary respect; it has also benefited in an economic way. The village is now one of the most prosperous in Germany, and has more than tripled its population since 1854.

Brehmer's literary contributions were not very voluminous, but what he wrote was of great value. I may mention here only three of his most important publications. Besides his doctorate thesis, above referred to, he published *Die Gesetze und Heilbarkeit der chronischen Tuberkulose der Lunge*, *Die chronischen Lungenschwindsucht, ihre Ursache und ihre Wirkung*, and *Mitteilungen aus Brehmer's Heilanstalt für Lungenkranke*. The latter was his last work; it appeared in May, 1889, in Wiesbaden, and also contains contributions by his four assistants, Wendriner, Stachiewicz, Stroschein, and Wisokowics.

Brehmer died on the 12th of December, 1889, mourned by thousands

of grateful patients, honored and esteemed by the profession, and venerated by the inhabitants of Goerbersdorf, to whose prosperity he had contributed so much. Those of the German population who knew nothing of the personality and inner life of Brehmer wondered that so great a physician never received any recognition from the Government, by either title or decoration, which meant so much in Germany at the time when Brehmer was alive. His independent and democratic views, which at the beginning of his career almost prevented him from carrying out his most cherished plans, were also the cause of the nonrecognition of his great services on the part of the Government. A beautiful monument to Brehmer was erected in 1904. It stands in front of the park leading to the sanatorium.

At the time of Brehmer's death there were three sanatoria in Germany and about the same number here in the United States. There are hundreds of them now, not only for the rich, but for the moderately and very poor as well, in all the civilized countries of the world. In our own country there is at this time no less than $200,000,000 invested in tuberculosis sanatoria and hospitals. We have nearly 700 institutions, sanatoria and special hospitals, which make available 66,000 beds for the sick from tuberculosis. The annual maintenance alone amounts to almost $75,000,000. While Brehmer was privileged to see the financial success of his own enterprise, his ardent desire,—the multiplicity of sanatoria for all classes of society,—he was not privileged to see realized.

Let the present generation of American physicians to-day, at the hundredth anniversary of the birth of this great pioneer in the prevention and treatment of tuberculosis and in the establishment of sanatoria for consumptive sufferers, give a grateful thought in memory of Hermann Brehmer.

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STUDIES ON TUBERCULOUS INFECTION[1]

XII. THE DISSEMINATION OF TUBERCLE BACILLI IN THE IMMUNE GUINEA PIG, WITH A DISCUSSION OF PROBABLE FACTORS INVOLVED IN TUBERCULO-IMMUNITY

ALLEN K. KRAUSE

In *Study VI* of this series (1) the paths of transit of tubercle bacilli in nonimmune guinea pigs had been exhaustively worked out and "charted." A leading inference from the work, and one which might justifiably be carried over to human tuberculous infection and pathology, in elucidating these, was that tubercle bacilli that are deposited in the lung normally find further passage to the tracheobronchial lymph nodes easy. If guinea pigs are made to inhale tubercle bacilli anatomic changes in the respiratory tract first come to view in the tracheobronchial lymph nodes (2) (3). If they are inoculated subcutaneously, the bacilli may be demonstrated earlier in the tracheobronchials, and frequently in larger numbers, than in the lungs (1). If they are of low virulence, and are inoculated subcutaneously, visible foci of the respiratory system usually appear only in the tracheobronchials (4).

A second deduction of consequence was that the transit of tubercle bacilli in the normal, nonimmune animal is extraordinarily rapid. Within four days after subcutaneous inoculation into the groin, the germs had reached the iliac lymph nodes, lungs, the tracheobronchial lymph nodes and the spleen; in other words, they had made the circuit of the body,—by superficial to deep lymphatics, to venous system, to pulmonary artery, to systemic circulation;—and, after having been deposited in the lungs, had, in part, been carried lymphatically again to lymph nodes,—the tracheobronchials. No doubt, factors of time and portal of entry will modify the rapidity of transportation, but the general principle of great ease and high speed of dissemination remains; that is, be it always emphasized, in the normal animal of native susceptibility and without allergy.

Upon the completion of the work mentioned, it was but a natural step to undertake an investigation, similar in several respects, on the immune

[1] From the Kenneth Dows Fund for the Study of Tuberculosis, of the Johns Hopkins Hospital and University.

or allergic guinea pig. Immunity to infection connotes bodily defense, and such defense suggests ideas of forces that operate through biochemical, physical or mechanical factors. With the rate of progression of an infecting agent determined with some precision for the normal animal, it was reasonable to presume that the disclosure of any significant alteration of this rate in the immune animal might take us a little closer to an understanding of tuberculo-immunity, at once the best-authenticated and the worst-explained fundamental fact of tuberculosis to-day.

Resolved into its elements, the problem of tuberculo-immunity, the question that demands answer, comes down, after all, to this: Does immunity operate in a way that destroys tubercle bacilli directly, or in a way that bars or retards their spreading in the body (or both)? There have been countless guesses, and not a few praiseworthy exercises of ratiocination from collateral evidence, to support either view; but, to the author's knowledge, there has as yet been presented no direct scientific confirmation, one way or the other, that is beyond criticism. The data derived from *Study VI* afforded at least an opportunity to look into the possibility of an altered facility and rate of spread of tubercle bacilli in the immune animal.

As the work progressed it encountered technical difficulties and variables which had to be met and accounted for. For instance, the active immunization of the animals involved their preliminary infection with one type (strain) of germs, while their testing required the application of a different strain, a circumstance which promised to obscure our results and made necessary the most accurate knowledge of the pathogenic capabilities of each microörganism.

Into the work, therefore, went three separate studies, each of which required the better part of a year in its performance. In the first, intracutaneous inoculations were used; in the other two, subcutaneous inoculations. Since all control animals were handled under exactly the same conditions as most of the test animals of *Study VI*, ample opportunity was afforded to repeat and confirm much of that investigation. Meanwhile, Willis traced the fate of tubercle bacilli in nonimmune and immune animals during the first few days after first infection and after reinfection, with results that are to be found in *Studies X* and *XI* of this series (5) (6). During 1924 and 1925, also, the summarized general findings of his studies and the present work, combined, were published as follows: *Trans. Nat. Tuberc. Assoc.*, 1924, p. 27; *Bull. d. l'Union Internat. contre la Tuberc.*, December, 1924, i, no. 3, 13; and *Tubercle*, 1925, vi, 438.

GENERAL REMARKS ON PLAN AND TECHNIQUE

After guinea pigs had been made allergic and immune by preliminary infection with R1 tubercle bacilli, the well-known Saranac Laboratory strain which after single inoculation will not cause progressive disease, they were to receive single reinfections with strain H37, a virulent strain. At the time of their reinfection, other normal, nonimmune guinea pigs were to be infected for the first time with exactly similar dosages of H37, of the same suspension; these were to serve as controls for the immunes.

Since we wished to discover the rate of dissemination of bacilli in the immunes, in other words, the time of first appearance of bacilli in various organs and tissues, further procedure was essentially the same as that pursued in *Study VI* in the comparable part of that work. This involved killing the guinea pigs at various intervals after inoculation with H37, removing the several tissues and organs desired, and inoculating these into new normal guinea pigs. If progressive tuberculosis developed in the latter animals it was proof of the presence of H37 in the inoculated tissue; failure to acquire tuberculosis meant that bacilli had not reached the reinoculated tissue by the time the latter had been excised from the "donor's" body.

In outline the technique of the inoculation of tissues was as follows: The infected animals were killed. Their bodies were immediately shaved and wrapped in cloths well-soaked with 5 per cent carbolic acid for never less than a half-hour and in most cases more nearly one hour. With the body still enclosed in carbolized cloths, and with just enough of it exposed at any one time to allow each operation, tissues would now be removed through three separate incisions. The tracheobronchial lymph nodes were always excised first, through the smallest possible opening in the midthoracic line; then the lungs through a more widely opened first incision; then the spleen through an incision in the left side beneath the ribs; and, last, the iliac lymph nodes through an opening in the lower half of the abdomen. The several operations therefore proceeded from regions where bacilli were presumably fewest to where they were most numerous. It is needless to say that at every step fresh relays of sterile instruments were used.

Upon removal each organ was placed in its own sterile mortar and thoroughly macerated by being ground over copper gauze. Taken up with as little physiological salt solution as possible, the pulp was then

inoculated into the groin of a normal healthy guinea pig. In this way each guinea pig, that was to serve as the indicator of tubercle bacilli in a tissue, received the whole of either (1) an iliac lymph node, or (2) the speen, or (3) all tracheobronchial lymph nodes, or (4) both lungs.

From now on the experiment involved, for weeks and months, the rather monotonous and laborious notation of frequent periodic examinations of all animals inoculated with tissue, and the continual tabulation of these observations. The appearance of characteristic bubo in the groin of an animal would be our first evidence that an inoculated tissue had contained tubercle bacilli. But continued observations could tell us more than this. In general, tubercle of first infection arises early or late, according as the bacilli concerned were more or less numerous; in general, also, the later vigor and local extent of development of tubercle run parallel with the original "dosage" of bacilli. By repeated examinations of the animals inoculated with tissue we could, therefore, gain an idea of the comparative numbers of bacilli contained in the several tissues at the time of their removal from the body; and determine, roughly though satisfactorily, whether at any time after virulent reinfection an animal's tracheobronchial lymph nodes harbored more or fewer bacilli than its lungs or any other organ. (See *Study VI.*)

Tissues were removed at intervals, from within four days to thirty days and more after reinfection. In general, four days after infection was set as the time of first investigation of organs because in *Study VI* we had learned that within these first four days after first infection bacilli had been carried to all parts of the body. Nevertheless, in the first experiment of the present study, in which inoculation was intracutaneous, the first excision of tissues was at twenty-four hours after infection, while in the last and most satisfactory experiment it was three days afterward. It is obvious that the shorter the time between infection and the removal of tissues, the less likely is an internal organ to contain bacilli; or, if virulent bacilli are present, the fewer are they likely to be. Because of their very few bacilli those inoculated tissues, which are excised soon after infection, may be extremely tardy in causing palpable changes (tubercle) in the groins of the inoculated animals, and, if tubercle does develop, it may evolve with extreme slowness. Instead of the two or three weeks, as observed ordinarily in experimental infection, it may take four or five weeks, and more, for the local inguinal lymph nodes to indicate a positive result. In these instances the involvement of the various internal organs may not become noticeable for months.

It is therefore necessary to carry the animals over exceptionally long periods, in order to allow time enough for tubercle to develop. Before we became sufficiently impressed by this fact there is no doubt that in a number of cases we terminated our observations too soon.

The use of immune animals in this study introduced a disturbing factor which did not enter into the work on the nonimmunes recorded in *Study VI*, and which had to be controlled thoroughly. The immune state was created through preliminary treatment of animals with living R1 bacilli. It was therefore to be expected that the tissues of such animals would always contain R1 bacilli in addition to any H37 bacilli, and that these R1 bacilli would set up tubercle upon the inoculation of any tissue. Since tubercle-formation in the animals which received tissues was to be our index of bacillary content of any tissue, we might be asked how we were to know whether the inoculated tissue carried over the R1 bacilli of immunization or the H37 bacilli of reinfection.

As a matter of fact, the R1 germs did frequently cause changes in the animals inoculated with tissue, a circumstance which in many instances led us to believe, for a while, that we were getting a positive result which only the later course of the infection proved to be false. This was especially true in the case of those tissues that were removed from immune animals within the first two or three weeks after reinfection.

For instance, characteristic palpable shotty enlargement of the superficial inguinal lymph nodes would begin to appear in a guinea pig at two or three weeks after it had had tissue from an immune. The event would be noted, and a record made of a probable positive result, that is, that at the time of the reinfected animal's death H37 bacilli had reached the particular tissue. The next two or three weekly observations would disclose these inguinal nodes as gradually enlarging, and our suspicion of H37 infection would be strengthened. The nodes might then remain stationary or they might diminish somewhat in size. If the latter, we would begin to doubt our earlier "diagnosis," change it tentatively to palpable R1 infection, and postpone final decision to the autopsy.

For it was only the autopsy of all animals, that had died an adequate time after inoculation, that would determine definitely which bacillus was concerned. *Study I* of this series describes the changes produced in guinea pigs by R1 infection with such detail as to make their repetition unnecessary here. In ordinary "dosage" and upon single subcutaneous inoculation the germ will not cause progressive tuberculosis or visible tubercle in internal organs. For the most part its noticeable effects

are confined to the nodes regional to the portal of entry and the tracheobronchial lymph nodes. On the other hand, when given enough time to develop, the changes brought about by H37 are progressive and will be found in the viscera.

We could therefore be certain that, in our test animals, any manifest tubercle which retrogressed later, or any tubercle localized only at or near the portal of entry signified infection due to R1. Indeed, our standard of H37 infection was laid down as follows: *A tissue can be said to have contained H37 bacilli only when its inoculation has led to unquestionable tubercle in an internal viscus. Lymphatic tuberculosis, without visceral tuberculosis, is to be recorded as probable R1 tuberculosis, and therefore a negative result.*

As it happened, these inoculations of tissues from immune animals, especially of those tissues excised soon after reinfection, yielded observations that confirmed strikingly the main generalization laid down in our *Study I*, although at the time this was derived from evidence of a totally different kind. *Study I* recited how, after prolonged infection with R1 bacilli, guinea pigs would exhibit lungs free from tubercle, yet display so much involvement of the tracheobronchial nodes as to make the latter appear the main ultimate *locus* of infection. From this observation was first deduced the hypothesis that free and open lymphatic paths in the guinea pig's lung promote an easy transmission of particles through it and on to the lymph nodes, thus making for a tracheobronchial rather than an intrapulmonary fixation (infection) of bacilli. When, now, the several tissues (iliac nodes, spleen, lungs and tracheobronchial nodes) of the immunes were inoculated into new guinea pigs, it was found that, in general, the tracheobronchials caused palpable *R1 infection* more often and to greater effect than did any other tissue. The only conceivable reason for this result can be that they more frequently contained R1 bacilli in larger numbers than the other tissues.

A second part of the plan of this study was to remove tissues from the immune animals for histological examination also. Although this material was collected, and some of it was prepared and gone over, the work was abandoned because of the difficulties of distinguishing R1 from H37 bacilli in stained sections. Therefore, while *Study VI* followed through the fate of tubercle bacilli detected microscopically as well as by animal-inoculation, this work has been based on data derived entirely by the latter method.

TUBERCLE BACILLI IN THE IMMUNE GUINEA PIG AFTER INTRACUTANEOUS REINFECTION

In *Study VI* all animals were inoculated subcutaneously, a procedure which infected them with comparatively large numbers of bacilli. When this work on immune animals was begun, the first series of H37 inoculations was intracutaneous, because it was thought that something might be learned from observing the immune reactions involved in the development of foci in a superficial location.

Thirty guinea pigs were made tuberculous (immunized) by subcutaneous inoculations (0.25 cc.) of a heavy suspension of R1 tubercle bacilli. Sixty-five days later, these animals, together with 30 new normal controls, were inoculated intracutaneously, each with 0.1 cc. of a centrifugated suspension of H37.

At 1, 2, 4, 5, 8, 9, 11, 13, 18 and 26 days after H37 infection, individual immune and control animals were killed, and the iliac nodes, spleen, lungs and tracheobronchial nodes of each were inoculated separately into normal guinea pigs as above described.

Results

Epidemic pneumonia wrought such havoc among the animals that not enough survivers remained to draw adequate comparisons between results in the several sets. Nevertheless, there were indications that transportation of bacilli to internal organs after intracutaneous inoculation was not so rapid as after subcutaneous infection. The gaps caused by untimely deaths make it uncertain just when bacilli may have first reached the lungs, spleen and tracheobronchial nodes of the controls,—those animals which were not immune. But our records would suggest that this was nearer the ninth day after infection than by the fourth day, which *Study VI* showed to be the case after subcutaneous infection. We have noted that the spleens removed from controls, eight days and later (ninth and eleventh days) after infection, caused H37 tuberculosis, but except for this the fragmentary findings give us little information concerning the tissues in either the immunes or the controls.

In *Study X* Willis has reported that tubercle bacilli are moved with extreme rapidity from the site of intracutaneous inoculation in normal nonimmune guinea pigs: within one to three hours they will have cleared the site of inoculation, and by twenty-four hours have reached the

regional lymph nodes. In general, therefore, mobilization of bacilli is swift and easy after both intracutaneous and subcutaneous inoculation. But the fact that in our experiments the two types of inoculation involved the introduction of different dosages of bacilli, namely, 0.1 cc. *into* the skin as against 0.25 cc. *beneath* the skin, should make some difference in the time of first appearance of bacilli in internal organs. Perhaps, also, the more compact tissue of the skin itself, if compared with the looser areolar subcutaneous tissue, might give rise to a relative retardation of movement of intracutaneously inoculated bacilli; but Willis's study would suggest that, if this does take place, it must be slight.

TUBERCLE BACILLI IN THE IMMUNE GUINEA PIG AFTER SUBCUTANEOUS INOCULATION

Two experiments were performed in which tissues, excised from immune animals that had been reinfected with H37 bacilli subcutaneously, were inoculated into fresh normal guinea pigs.

1: Fifteen guinea pigs were infected subcutaneously in the right groin with 0.5 cc. of a heavy emulsion of R1. Fifty-eight days later, together with 20 normal controls, all animals received 0.25 cc. of a fairly rich suspension (15 to 20 bacilli per oil-immersion field) of H37. Left iliac node, spleen, lungs and tracheobronchials were excised, as described above, at 4, 6, 9, 12, 15 and 20 days after H37 infection, and separately inoculated into normal guinea pigs.

Results

Tissues from the *nonimmune* controls first caused H37 tuberculosis in the test animals as follows:

The left iliac node removed four days after infection.
The spleen removed six days after infection.
The lungs removed six days after infection.
The tracheobronchial nodes removed fifteen days after infection.

The tissues from the immunes to produce infection first, were:

The left iliac node removed at six days.
The spleen removed at twelve days.
The lungs removed at twelve days.
The tracheobronchials did not set up infection in a single instance (up to twenty days).

Since the tissues of only one animal of each set were inoculated at the different periods after infection, the material was thought to be too scanty to warrant final conclusions, and plans were made to repeat it on a larger scale. Nevertheless, the general result did point to a retardation of spread in the immune animals, and another fact appeared which was still more definite and suggestive. This was that, in the case of the nonimmunes, once a given tissue was found to cause H37 infection, the same tissue, removed from other animals later, always produced tuberculosis, while *visceral* tuberculosis was caused by internal organs from the immunes in only one instance, that of the twelve-day guinea pig, whose spleen and lungs were both positive. In no case were the spleen, lungs and tracheobronchials infected when excised from animals earlier than twelve days, or at fifteen and twenty days after infection. Notwithstanding the paucity of animals, this circumstance suggested that the retardation of spread of tuberculosis in the immune animal is greater than we had anticipated, and that in repeating the experiment we would have to extend greatly the periods after H37 infection for the excision of tissues.

2: Accordingly, the next experiment began with 41 guinea pigs immunized with R1 in the usual way and 36 normal controls, each of which was subcutaneously infected in the groin with 0.25 cc. of a suspension of H37, turbid and milky in appearance but bacillary content not estimated.

Tissues from *two* immune and *two* nonimmune guinea pigs were removed and inoculated separately into normal guinea pigs at 3, 5, 7, 10, 13, 17, 21, 31, 40, 48 and 69 days after H37 infection. The tissues were the usual ones, that is, iliac node, spleen, lungs and tracheobronchials.

Results

Tissues from the *nonimmunes* were found to cause tuberculosis as follows:

The iliac nodes removed from both animals three days after H37 inoculation, and always afterward.

The spleen removed from one animal at three days, from one at five days, from one at seven days, and always afterward.

The lungs removed from one animal at five days, from one at seven days, and always afterward.

The tracheobronchials removed from one animal at seven days, and always afterward.

In the case of the immunes tuberculosis resulted as follows:

From the iliac node (slight infection) removed from one animal at three days, one at five days, one at seven days, and always afterward.

From the spleen removed from one animal at ten days (slight), one at thirteen days, one at seventeen days (slight), and always afterward. The spleens from both animals at three days, both at five days, both at seven days, one at ten days, and one at thirteen days were negative.

From the lungs removed from one animal at thirteen days (before this all lungs were negative), one at seventeen days, one at twenty-one days, both at thirty-one days, both at forty days, and both at forty-eight days. The lungs sixty-nine days after inoculation were negative, as were also those from one animal at seventeen days and one at twenty-one days.

From the tracheobronchial lymph nodes removed from one animal at seventeen days (all negative before this), one at twenty-one days, both at thirty-one days, and both at forty days. The tracheobronchials at sixty-nine days were negative.

Summary of Results of Subcutaneous Experiments

In summary, the findings of these two experiments may be stated as follows:

In control or nonimmune animals: Given sufficient original "dosage" of tubercle bacilli, inoculated subcutaneously, there occurs a dissemination to all parts of the body within the first week after infection. Indeed, in most instances this probably takes place within three to five days afterward. One of two animals of the second subcutaneous experiment had bacilli in its spleen at three days after inoculation; one of two had them in the lungs at five days; and one of two, in the tracheobronchial nodes at seven days. From ten days on, bacilli could always be shown to exist everywhere. Such a result substantially confirms those reported in *Study VI* in regard to the rate of distribution of tubercle bacilli throughout the body of the nonimmune guinea pig. For in *Study VI* it was laid down that by four days and earlier bacilli reach the iliac nodes; by four days and *perhaps* earlier, the spleen; and by four days, the lungs and tracheobronchial lymph nodes. A difference of two or three days either way in the case of any individual organ or tissue is of no moment as affecting the validity of the general deduction that has been made. *A nonimmune guinea pig experiences generalized dissemination of tuberculous infection with great facility.*

In immune animals: In these guinea pigs some bacilli may be carried to the iliac lymph nodes, near the portal of entry, within three days after a groin inoculation, but it is only from about ten days on that they are to be found in these nodes regularly. This period may be contrasted with three days, which we may set as the maximum time of uniform localization of germs in the iliac nodes of the nonimmunes.

In the case of the spleen it would seem to be a matter of about ten days after infection for the occasional appearance of bacilli, and about twenty-one days before bacilli may be expected to be present regularly. Again, the spleens of the immunes removed at ten, seventeen and twenty-one days in this experiment set up a very tardy and slight tuberculosis in the animals inoculated with them, an event which indicated the slight bacillary content of the inoculated organs. On the whole, we may say that a journey, which can be accomplished in three days in normal guinea pigs and is never delayed beyond ten days, takes from ten to twenty-one days in immune guinea pigs.

Similarly, the five to ten-day trip from groin to lungs and tracheobronchial lymph nodes in nonimmune guinea pigs is lengthened to from thirteen to thirty-one days in the immunes. Although they may be found earlier in these tissues, bacilli are always present there by ten days in nonimmunes; while, although they may have reached the lung and its lymph nodes of the immunes by from thirteen to seventeen days after inoculation, it is not until about thirty-one days that we may be certain of finding them there.

GENERAL DISCUSSION

Early in this study we formulated, as fundamental to precise concepts of the mechanism of tuberculo-immunity, the following question to be answered:

Does immunity operate in a way that destroys tubercle bacilli directly, or in a way that bars or retards their spreading in the body (or both)?

From the evidence which has just been presented it is established beyond doubt that after their entrance into the body of immune guinea pigs there occurs a marked delay in the time of first appearance of tubercle bacilli in the various tissues in which they are accustomed to localize. At the same time, as will be brought out more fully below, after visceral localization does occur the bacilli are relatively (as compared with nonimmunes) few for a considerable period.

It is obvious that such a delay of passage of germs from place to place, and such a diminution of bacilli that are mobilized, will result in anatomical (pathological) effects which create for us the representation of immunity,—of fewer and more limited and more sluggish foci. It may therefore be permitted to wonder whether the active elements of what we call immunity are not whatever may bring about this slowing up and lessening of bacilli.

Without further analysis, one may think of either of two possibilities as leading to the result noted: either, that, without necessarily destroying bacilli, new tissue reactions are interposing more or less effective barriers to the spread of bacilli; or, second, that some immune agent is destroying bacilli, which, now reduced in number, can be found in internal organs only after a considerable prolongation of that period which is established as ordinary for the nonimmune animal. For we consider as settled the general proposition that, altogether apart from any other factors, immune or otherwise, the time of first appearance of tubercle bacilli in an internal *locus*, which is separated from the point of entry by normal lymphatic tracts, will be influenced by such a factor as initial dosage of bacilli. Between a portal of entry and an interior point is always a variable number of collections of lymphoid tissue (lymph nodes, etc.), each of which, in a continuing path, has undoubtedly its own capacity of intercepting completely particles that are being moved by the lymph, a value which, in terms of numbers of particles, we may designate by x. Accordingly, if the kinetic energy of the lymph-flow remains constant, the time of appearance at more and more central points, the distances of which from the peripheral point of entry increase, must vary inversely as the number of particles exceeds x; that is, it will become shorter as the number of bacilli in transit increases.

With such considerations before us, we may examine the data at hand.

In considering immunity to an infection nothing is more natural than, without further evidence, to think of it working through a specific lysis or destruction of bacteria. Such an idea is not only in accord with current concepts of *a* mechanism of immunity, but certain facts support it. There is the *Pfeiffer phenomenon*, to be observed in the case of several bacteria other than the tubercle bacillus, while Bail's *aggressins* in tuberculo-immunity represent simply a varient of the Pfeiffer phenomenon. In extensive (though unpublished) observations that included the histological examination of foci of cutaneous reinfection, I have had ample opportunity to note the rapid disappearance of tubercle

bacilli of reinfection *in situ*. Similar occurrences have been reported by Rist and Rolland (7), who at the same time describe a fragmentation of bacilli that was not so apparent to me. All that I could observe was that within a few hours after reinfection I could not discover many tubercle bacilli (after carbol-fuchsin staining) in places where I expected to find them.

According to our more modern concepts, pleural, meningeal, peritoneal and articular effusions are to be regarded as allergic responses to metastatic reinfection, and may therefore be regarded as immunity reactions. When Paterson examined the allergic nature of the pleural response to local reinfection (8), he also found tubercle bacilli to be few or nonexistent in the fluid poured out immediately after local reinfection; and this observation pointed to a lysis of bacilli. On the other hand, Paterson found these same fluids highly virulent upon their inoculation into test animals; and such an event suggested a modification of staining qualities or of familiar morphology of bacilli rather than the latters' destruction. Performing essentially the same experimentation on the peritoneum, Rist, Rolland and Kindberg (9) did find, contrary to Paterson, a sterilization of more than half of a series of peritoneal exudates in allergic animals. Manwaring and Bronfenbrenner (10) conclude, from histological evidence, that tubercle bacilli disappear from serous-cavity effusions; but they do not support their conclusions by findings obtained by inoculation of the fluids.

In clinical practice it is notorious how difficult it may be to find tubercle bacilli in such effusions when they are of serous character, a circumstance that would favor the idea of lytic action. But it is just as notorious that when the effusions are highly purulent they may abound in bacilli. Indeed, except in particles of caseous tissue (rice bodies) spat up from the lungs or passed with the urine, I have never seen tubercle bacilli so numerous in clinical specimens as in a few cases of suppurating pleurisy with effusion. A purulent tuberculous pleural effusion can be no less the result of an immune response than is a serous effusion. If each represents an immunity reaction, it can only be that the purulent fluid is the resultant of a more intense and vigorous reaction, exactly as a cutaneous reaction to *tuberculin* with necrosis and pus is a more severe reaction than one to tuberculin with simply hyperemia.

We see, therefore, that, in interpreting clinical or experimental phenomena, we run into contradictory difficulties as soon as we extend our observations beyond the elementary one of noting a physical alteration

or disappearance of characteristic bacillary forms. This is in no respect a novel experience in so called "lysis experiments." For years those who have based positive reports of lysis of tubercle bacilli on histomorphological findings alone have uniformly been met with the criticism that their work was insufficiently controlled, and that adequate observations on bacilli that had been subjected to indifferent reagents, or on bacilli taken from cultures on various media and of different ages, would disclose a beading, or fragmentation, or faint staining of bacilli that was not particularly dissimilar to that noted in their lysis experiments.

Before we may come to a more correct opinion of this whole subject, it is important that we understand just what we mean by *lysis* in immunity, especially in tuberculo-immunity; for it would appear that much of our difficulty has resided in our failure to define our terms. Obviously, the word connotes a breaking up or, more precisely, a dissolution of bacteria. But, as applied to immunity, it must denote something more than this, if it is to have any special significance at all. It seems to the author that it must then imply, after the proper proof has been adduced, that, as part of the operation of the immune state, there is brought about a dissolution of tubercle bacilli by agents that are specific components of the immunity mechanism. That is to say, such agents are motivated and appear only in immune animals, or they are to be found in characteristic excess only in immune animals. For it is only common sense that, if *lysins* are at work in animals other than those which are immune, we had better give up the term *lysin* as designating an agent that is one of the several constituents of the apparatus of specific immunity, or as implying that it acts only in specific immunity.

If we take this position we may be hard put to it to discover any adequately controlled work that has satisfactorily demonstrated specific tuberculo-lysins. What will make the demonstration of unquestionably specific lysis all the more difficult is the easily ascertainable fact that tubercle bacilli disintegrate under the influence of nonspecific substances, some of which, or some similar to them, quite likely commonly exist or originate in the animal body, whether this is immune or nonimmune.

For instance, if living tubercle bacilli are kept in physiological salt solution at body temperature they will rapidly undergo physical disintegration. Under such conditions we shall see a turbid suspension clear within a few days, and find it difficult to detect typical acid-fast

rods which originally were abundant. Yet such a suspension will be still highly virulent.

According to the standards usually employed to establish an action by lysins, that is, the fragmentation and physical disappearance of characteristic tubercle bacilli, there takes place a lysis of the germs in this thoroughly indifferent medium. The reason for this is not clear; the most likely one would attribute bacterial disintegration to an *anisotonicity* of the menstruum. Indeed, it is only rational to suppose that within the animal body microörganisms come to reside in fluid or semifluid media, the tonicity or physical nature of which is incompatible with the preservation of their corporeal integrity.

Baldwin once put the commonly held idea of certain blood-sera possessing tuberculo-lytic powers to rather rigorous testing; indeed, his sketchy account (11) of his work on the bacteriolysis of tubercle bacilli and on the bactericidal powers of sera gives no impression of the comprehensiveness of his experiments. He used sera of animals which are undoubtedly immune to tuberculous infection, as we ordinarily understand the term. He arrived at results which could not be regarded as lying outside the range of the effects of technical difficulties, a fact which he mentions. He could demonstrate no bacteriolysis exerted by the incubated serum of normal or tuberculous (immune) animals on living or dead tubercle bacilli.

One might readily understand how an effusion, called forth by allergic response to reinfection, could bring about the destruction of bacteria and yet be entirely lacking in any specific antibacterial lytic substance; just as one can imagine how an effusion arising in any manner whatever might be bacteriolytic although the blood-serum of the same animal might not be so.

Effusions are derived through exudation of the blood-serum. We know that they vary from the latter in specific gravity, in tonicity, in concentration of solids, etc. In all these elements, also, they vary among themselves, according as the stimulus (virulence and dosage of bacilli, etc.) and the reactivity (degree of allergy) have been greater or less. One would only expect, therefore, that *on physical grounds alone* effusions would nonspecifically be more or less favorable (unfavorable) for the preservation or multiplication of contained bacteria. It is not meant for a moment that the action of immunity in tuberculosis does not comprehend the release of more specific lytic elements (together with a host of other factors). What is suggested is that through the operation

of allergy, a specific immune phenomenon, there evolves a series of physical conditions, which, at one or more stages, can be nonspecifically destructive for tubercle bacilli and lead to the same observable effects as specific lysins. Practically, any agitation of the matter may seem a quibble; if, however, we are to understand immunity, its elucidation is highly important.

We can imagine, further, other conditions, thoroughly nonspecific so far as immunity is concerned, continually arising to promote or hinder the breaking up of tubercle bacilli within the body. To mention only a few, there are, for instance, the ceaseless transformations of the structure of the foci, their increasing fibrosis or softening, with their consequent less or greater penetration by body fluids and resulting alteration of the physical environment of the bacilli. There are the nonspecific ferments, released whenever tissue changes set into play the proper chemical processes. There are, presumably, other chemical changes, such as the deprivation of available oxygen in suitable form. Every person who is at all experienced in the bacteriology of tubercle bacilli must be impressed by Corper's *idea* of searching for the therapeutic *tuberculocide* via some method that will cut off the bacillus's oxygen,—in particular, by substituting carbon dioxide for it (12) (13). The observant laboratory *Diener* soon learns that he can materially enhance the growth of his tubercle bacilli by occasionally removing the plugs of his culture-tubes, so as to allow air to enter, or by merely loosening the plugs for a while. There is nothing at all doubtful about the great need of tubercle bacilli for oxygen; and we must believe that, deprived of it, they will at last die and disintegrate. Just how the bacilli metabolize tissue oxygen, through what materials and in what chemical combinations it can be used by them, we do not know. No fundamental research on the biology of tubercle bacilli would seem more promising of useful practical application, and the start recently made in this direction by Novy (14) is to be commended.

Accordingly, it would seem certain that a lysis of tubercle bacilli must be going on interminably in the body under conditions that have nothing to do with *specific* immunity. Bearing such possibilities in mind, and mindful also of the great difficulties of controlling those morphological studies that would seek to determine lysis by observing histological changes of the bacilli, as well as the difficulty of making sure that any changes (granting that they are accurately detectable) are the resultant of specific immuno-lysins in any or every case and not

the effect of nonspecific processes,—with all this before us, it is certainly open to question whether we have had convincing evidence of the actuality of immuno-lysins in tuberculosis.

To return to the interpretation to be put upon the data of our experiment. These proved decisively that in immune guinea pigs the transmission of tubercle bacilli from point to point is greatly delayed. And, in the effort to discover whether this more tardy first appearance of bacilli was brought about through their destruction at more peripheral points or through their temporary arrest by mechanical barriers, recourse was had to another method of analysis of our findings.

It has already been mentioned how we can get some idea, rough though it may be, of the number of bacilli in a tissue at any time, by observing the time of first appearance and the vigor and extent of evolution of the tuberculosis caused in a fresh guinea pig by the inoculation of the tissue. Our index of first appearance of disease is that time when palpable involvement of the inguinal (the regional) lymph nodes in the animal inoculated with tissue first becomes appreciable. Our opinion of the more or less rapid and extensive course of the disease is derived from periodical observations of the tissue-inoculated animal during life and from an autopsy at death.

When a fairly large "dose" of H37 tubercle bacilli from cultures is inoculated subcutaneously into the groin, the inguinal lymph nodes usually begin to show definite changes toward the end of the second or in the third week after infection, and generalized tuberculosis will be manifest at autopsy from about four weeks and later after infection. This sequence has become a sort of standard of ordinary routine experimental infection, and may serve as a basis of comparison.

In the *Summary* of results of the second subcutaneous infection above it was mentioned that in immune animals tubercle bacilli were found in iliac nodes once (out of two animals) at three, five and seven days after H37 infection, and in all cases afterward; while in the iliac nodes of nonimmunes they were always present from three days on. It will be remembered that the iliac nodes are situated at the bifurcation of the great abdominal trunks into the common iliac vessels, and are the first main "stopping place" within the body for bacilli put into the inguinal areolar tissue. Between them and the site of inoculation lie the superficial and the deep inguinal lymph nodes.

In the case of the iliac nodes removed from the nonimmunes and inoculated into new animals, that removed at three days after infection from one animal gave rise to inguinal-node tuberculosis that was first recorded as positive at seventeen days, and that from the other animal at twenty-four days. Both animals had extensive tuberculosis at autopsy. All iliac nodes removed later produced tuberculosis with similar time relations. These findings bespoke a fairly large H37 content for the iliacs of the nonimmunes as early as three days after infection.

The guinea pig inoculated with the iliac node of one three-day immune never developed tuberculosis, and was free from it ninety-three days after tissue inoculation. The animal that received the iliac node from the second three-day immune never displayed palpable changes in its superficial inguinals. At autopsy, ninety-three days after tissue inoculation, it had a minimal amount of tuberculosis,—fibrosis in the groin, one small nodule in the spleen and one minute fibrocaseous focus in one lung. To produce so slight an infection, the iliac must have had extremely few bacilli.

Iliac nodes removed from immunes later produced first noticeable groin tuberculosis as follows:

One five-day iliac at twenty-two days.
One seven-day iliac at twenty-three days.
One ten-day iliac at twenty days.
One ten-day iliac at twenty-five days.

All iliacs removed from the immunes earlier than ten days after infection set up only the slightest visceral tuberculosis, found at autopsy about ninety days after tissue inoculation. The iliacs of all nonimmunes gave rise to very advanced disease.

The spleens from the nonimmunes would produce palpable inguinal tuberculosis during the third week after their inoculation: in all cases the resulting tuberculosis was extensive at autopsy. The first spleen from an immune to be infectious was removed ten days after H37 infection. A first positive result from it was recorded sixty-six days after its inoculation, and the animal which received it was found to have slight tuberculosis ninety days after inoculation.

The next spleen from an immune that produced tuberculosis was one removed thirteen days after H37 infection. Through an oversight it

was inoculated into a pregnant guinea pig, that was gravid when inoculated. This animal first showed inguinal tubercle at twenty-six days, and at autopsy, ninety days after tissue inoculation (having littered meanwhile), was found to have fairly extensive tuberculosis. Tuberculosis caused by the one positive seventeen-day spleen became noticeable first at forty-five days after tissue inoculation, and turned out to be very slight at autopsy, ninety days after inoculation.

The lungs from one five-day nonimmune were quite slow in setting up tubercle in the tissue-inoculated animal,—a first positive reading was not obtained for fifty-seven days; but at autopsy, ninety-one days after inoculation, fairly extensive tuberculosis was found in the animal that had received tissue. Both lungs and tracheobronchial lymph nodes, removed from nonimmunes ten days and later after H37 infection, always gave rise to extensive tuberculosis which would begin to appear from the third to fourth week after tissue inoculation. The few lungs and tracheobronchials, removed from immune animals earlier than thirty-one days after H37 infection, which produced tuberculosis on inoculation, set up but slight tuberculosis.

The more closely one examines the step-like evolution of tuberculosis in the animals, and compares the time of appearance from place to place in the two sets and the final results at autopsy, the more one becomes convinced that, in the immune animals, there has occurred a material reduction of bacilli that reach the several tissues, besides a delay in their arrival at the various points.

Now the same numbers of bacilli were inoculated into the members of the two series of animals. A reduction of bacilli could be caused by lysis at the portal of entry; it could also be affected by the prompt interposition of a barrier there. The evidence for and against immunolysis in general has been presented above. There is still another almost uniform result of reinfection experiments that has always seemed to the author to weigh heavily against the probability of an immuno-lytic activity being responsible for the more chronic and less severe disease that follows reinfection in the immune animal.

This is that some bacilli surely survive, even though their original number is small. If one reinfects (in the skin, say) a highly allergic tuberculous animal, some local tubercle follows (see Krause and Peters (15)). If it is true that the allergic response is accustomed to kill off by immuno-lysis such large numbers of tubercle bacilli as would be

concerned in experiments as conducted by Paterson, it is almost impossible to understand why it does not destroy *all* the bacilli introduced in experimental reinfection. I have never yet made an inoculation of reinfection into the skin of a tuberculous guinea pig without having some nodular tubercle develop in the site after the acute inflammation of allergy has passed; and I have convinced myself that this nodular tubercle is not the resultant of dead bacilli—that is, bacilli killed by lysins. It undoubtedly arises from living survivors of the local reaction. Besides, *lysis* implies disintegration and dissolution; and for nodular tubercle to be called forth by dissolved bacilli makes necessary the introduction of entirely new concepts into our ideas of the histogenesis and pathological anatomy of tuberculosis. Dead tubercle bacilli may set up tubercle if "dosage" is sufficient; but they certainly will not do so if they are far degraded and dissolved.

I have previously called attention to the difficulty of squaring this circumstance with any idea of lysis (15) (16). Lysis will explain a retardation of metastasis of bacilli from point to point; it will account for a thinning out of germs, and their consequent delay of appearance in appreciable numbers in internal viscera; but in the way of its acceptance as an explanation, stand, as have been set down here, too many conflicting ascertainable facts.

On the other hand, the idea of a mechanical barrier thrown up around the new bacilli of reinfection will also account for the retardation of spread of bacilli in the immune animal. Any interposed obstruction to the passage of bacilli along normal paths of dissemination would also thin out the number of bacilli that normally would get to a more central point.

The merit of such an explanation of the operation of immunity is that it has much authenticated fact to support it. As the author has so frequently pointed out (15) (16) (17) (18), the prompt response of allergy, that meets reinfection *in situ* in all immune animals, may be conceived as acting in such a way as to fix or confine reinfecting bacilli almost immediately at the place where they localize. The restraining zone of inflammation is, of course, only relatively effective. In *Study XI* of this series (6) Willis has shown that by the end of two weeks some reinfecting bacilli, alive and with virulence unimpaired, do make their way out of and past the site of reinfection and on to the first chain of lymph nodes,—a further proof, moreover, that if a lysin has been at work

it has not succeeded in destroying all of the few bacilli applied in intracutaneous infection of the immune animal.

Theoretically, at least, an allergic animal should at once throw out an inflammatory zone at every point where tubercle bacilli lodge, and englobe them with it. This will, of course, impede their further progression, at least temporarily. But it should also affect, no doubt unfavorably, their normal opportunity to draw from the tissues whatever sustenance is necessary, and thus influence their development and multiplication. It is in some such terms, that are anything but precise, that we would tentatively, and for the present, explain what happens in the allergic and immune animal when bacilli are experimentally introduced. For bacilli are fixed *in situ* and their further spread is retarded or diminished,—there can be no doubt about that. But again there is no doubt that bacilli remain alive. And it would appear that what actually happens to these surviving bacilli is that they multiply slowly, if they increase their numbers at all; that their foci have all the earmarks of chronicity, with fibrosis prominent as they remain discrete; that in time healing may take place; and that necessary to any acute or fulminant development is an eruption into a major channel of spread. Always important in any consideration of immunity, we may repeat, is the fact that in all these phases,—in even the best-arrested tuberculosis, in even many an old fibrocalcareous focus, in even a remarkably well-healed fibrous scar,—*the bacilli remain alive;* a fact which concepts of specific bactericidal immune substances must explain satisfactorily, if they are to be accepted.

In this connection may be cited observations of Theobald Smith (19), made upward of ten years ago, which would seem very suggestive.

Every bacteriologist knows that if cultures of tubercle bacilli are not transplanted to new tubes there comes a time when they can no longer be successfully subcultured. It used to be taught that six months of incubation was about as long as they could go without renewed subcultivation; that, if transferred to fresh media after that time, they would produce no new growth. However, I have in one instance successfully transplanted tubercle bacilli, which had been kept undisturbed for ten months on Dorset's egg medium and which were of the first culture derived directly from the pus of tuberculous lymphadenitis. Nevertheless, subcultivation from the second generation after six months' incubation failed.

It had always been assumed that the bacilli of these old cultures, which failed to continue growing on subcultivation, had died out. But Smith showed that such was not necessarily the case. He had put such old and apparently dead cultures in the icebox for as long as nineteen months and had then inoculated them into guinea pigs. He then found that some of these animals developed progressive tuberculosis, and that fresh cultures from the animals' tissues would proceed with viability apparently unimpaired.

Smith asked whether it was not possible that, to meet the changing reaction (perhaps the increasing acidity) of the medium, the bacilli elaborated a protective substance (coating?), and went into a resting stage, so far as their life on culture media was concerned. Perhaps, then, when the bacilli were inoculated into animals, they would multiply anew as they found their environment more favorable to their growth. We might, in a way, think of such bacilli as seeds, endowed with a capsule or other protective apparatus and dormant for years, yet capable of germinating whenever they strike contact wth the proper soil and stimuli.

We may be allowed to indulge in similar fancies when we are confronted with those puzzles which some of our most common facts of tuberculosis present. For instance, we know that a capable specific tuberculo-immunity will withstand and do away with large numbers of virulent bacilli. Here, then, is an animal (or person) with demonstrated high immunity; it takes care of much tuberculosis well, and the latter clears remarkably; immunity can be proved to remain high; yet a very few minute foci with living tubercle bacilli persist; nor do these bacilli multiply appreciably; yet they live on indefinitely. If the bacilli survive they must presumably draw some sustenance from their environment. If they can do this, why are they not also accessible to specific destructive agencies (lysins) in the body juices, if such agencies exist?

But, one thing we are certain of, and this is that the future fate of the bacilli interned within the foci turns on what happens to the investment of the focus. If it fails to "hold tight,"—and clinical experience teaches us amply that physical strain, for instance, can make a breach in the focal investment,—if it gives way, then bacilli may escape; and if they are moved outside, and on to new points, again and again do we find them multiplying and setting up new foci, in animals, be it remembered, that are always immune. Why cannot these animals, if they possess immuno-lysins, kill off the very few germs that are transferred to fresh

soil, where now they must surely be accessible to all serum "immune bodies?"

The answer must be obvious. The animal body remains the same; the body-fluids remain the same; the tubercle bacilli remain the same; but as regards the relation between bacilli and body it makes all the difference in the world as to whether the bacilli are held within a good fibrous wall of a tubercle or have been let loose on new soil.

We may conclude this *Discussion* by relating the fate of several immune animals included in the above experiments and kept for prolonged observation; for it would seem to illustrate beautifully in broad outline some such sequence of events as we have been trying to build up.

Ordinarily, in conducting immunity studies we terminate the experiment by killing all animals several months after inoculation, compare the findings in both nonimmune and immune sets of animals, and appraise the immunity of the one set from this comparison. Experience had taught us to make this comparison, as a rule, at from two to four months after infection; for by this time the nonimmune controls should have extensive tuberculosis and could not be expected to live much longer.

By this time an immune animal will never have died of tuberculosis. Usually, the immunes then show either no visceral tuberculosis, or a very few scattered visceral foci; and from a long experience we had come to believe that such immunes would survive indefinitely without ever developing progressive and fatal tuberculosis. Nevertheless, we never tested this opinion by carrying the animals in the laboratory for more than a few months.

In the above experiment, we saved some of the immune animals for observation long after the H37 inoculations had been made. The last tissue inoculations were made with tissues removed sixty-nine days after H37 infection. At this time the nonimmune had extensive tuberculosis everywhere in the body; it was therefore unnecessary to inoculate its tissues in order to determine the presence of tubercle bacilli in them. But an immune was found to be without visible visceral tuberculosis. Its spleen was found to be positive on inoculation, while no disease resulted from its lungs or tracheobronchials.

One hundred days after H37 infection there were a very few minute foci in the spleen and lungs of three immune animals killed for observation of the progress of infection. At one hundred and thirty days no

advance over the condition in the preceding animals was to be made out in two more immunes that were killed.

There were now two survivors of the immune group; all nonimmunes had either been killed (for tissue), or had died long before. One of these two survivors died almost ten months (lacking five days) after H37 infection. It was completely tuberculous with advanced disease, from which it had died. The other animal lived a month longer, and died exactly eleven months after H37 infection. It also had succumbed to the tuberculosis, as it was found to have extensive generalized disease.

Such a sequence of events clinches as conclusively as can be, through an experiment of this kind, that tuberculo-immunity is accomplished not so much through a wiping out of bacilli by specifically antagonistic substances as by through their being held in measurable check at various points and hindered from spreading throughout the body. It shows that if one originates virulent infection with bacilli enough to overcome a guinea pig's immunity, the progression of infection will be delayed to such an extent that it will be lengthened out from three to four times what we may regard as its normal period of evolution throughout the body.

No doubt the most important check to progression,—one might almost say the decisive one,—is that encountered at or near the portal of entry at the time of reinfection, when, of course, "dosage" of infection will also play its part. But, if allergy works with sufficient speed and vigor, the resulting reaction should frequently succeed in blocking all new bacilli completely and permanently; whereupon, the fibrous tubercle that follows allergic inflammation may keep a few living bacilli confined for all time, or the bacilli, gradually disintegrating under unfavorable conditions of physical environment, may disappear and the focus heal.

In any event, a given number of bacilli, capable of producing a given result in nonimmunes, will have suffered a relative check. In any event, fewer bacilli than in the nonimmune can be carried further into the body. And, now, wherever these bacilli that have got by the first obstacle are deposited, there too will they at once meet with an allergic reaction, and undergo further hindrance; and so on.

That the mechanism works is proved by the vast proportion,—perhaps ninety-nine per cent,—of all infections with virulent bacilli that never become significantly progressive. And when they do, we may be sure that in most instances it is because outside influences, the contributing

etiological factors of tuberculosis, have been at work to disturb and upset the defensive structure of the foci or the proper functioning of the allergic state. These may be measles or influenza or physical exhaustion, depressing allergy; or they may be excess of effort with its physiological reaction on the tissue of the focus.

SUMMARY

1. In the immune guinea pig, after virulent subcutaneous infection there occurs a great delay in the transmission of tubercle bacilli from the point of entry to the customary places of localization of bacilli within the body.

2. There is, besides, a localization in the various tissues of fewer bacilli than takes place after similar infection of nonimmune animals.

3. There are, presumptively, two possible explanations to account for this retardation and diminution of bacilli in immune animals, as follows:

a. They are brought about by specific immuno-lysins which destroy the bacilli, or

b. They are due to the prompt interposition of a barrier, which checks, at least temporarily, the further spread of bacilli.

4. The probabilities for and against immuno-lysis of bacilli are discussed.

5. The experimental data presented, together with other considerations, are believed to weigh against any interpretation which would make immuno-lysis decisively responsible for the results observed.

6. It is believed more probable that, upon being reinfected, the tissues of the immune guinea pig react promptly with some process that serves to impede the further passage of bacilli.

7. It is submitted that this process is the allergic exudative or inflammatory reaction, which invariably sets in upon reinfection of the tuberculous immune guinea pig which is otherwise normal.

8. Immune guinea pigs, which for months are relatively refractory to progressive tuberculosis, will eventually yield and succumb to it.

9. The outstanding and significant feature of tuberculo-immunity in guinea pigs is therefore not so much the complete inhibition of the activities of tubercle bacilli as a retardation of their spreading within the body.

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STUDIES ON TUBERCULOUS INFECTION[1]

XIII. THE TRACHEOBRONCHIAL LYMPH NODES OF THE RABBIT AND THEIR BLOOD SUPPLY

HENRY STUART WILLIS

During the progress of these *Studies* the impression was gained that normally there is a paucity of extrapulmonary lymphoid tissue in the rabbit. Krause has noted the circumstance in his *Study VI* (1), when he remarked that, although guinea pigs have little lymphoid tissue within the lungs, their tracheobronchial lymph nodes are relatively large and prominent, while rabbits exhibit exactly opposite relations, that is, much intrapulmonary lymphoid tissue and small and insignificant tracheobronchials.

The present study has sought to examine the relation of tracheobronchial lymph nodes to the lungs in rabbits more comprehensively and more exactly than was permitted by observations made in other experiments of different design. It has worked over a material consisting of the lungs and tracheobronchial nodes of upward of two hundred rabbits, many of which were also examined microscopically.

Very noticeable, as mentioned by Krause, are the small size and inconspicuousness of the rabbit's tracheobronchials. They may even be absent or unrecognizable; and, in about 20 per cent of the rabbits examined, they were present only in microscopic size. When visible, they are not as large as those of the guinea pig, although the volume of the rabbit's thoracic cavity (and therefore its lungs) is approximately five times the size of that of the guinea pig.[2]

These small nodes ordinarily measure about $5 \times 2 \times 1$ mm., and are

[1] From the Kenneth Dows Fund for the Study of Tuberculosis, of the Johns Hopkins Hospital and University.

[2] This volume was determined by inserting a needle through the chest-wall of normal rabbits and guinea pigs of various ages and sizes, and injecting water until a moderate distention of the thorax was produced, as the lungs were meanwhile collapsed by the fluid. The average weight of a wide range of rabbits was 2150 gm., and the average thoracic capacity 200 cc., while for a large number of guinea pigs the average weight was 465 gm. and thoracic capacity 41 cc. Because the rabbit's mediastinum is imperforate its thorax had to be injected in both sides; but in the guinea pig both sides of the thorax were filled with a single unilateral injection.

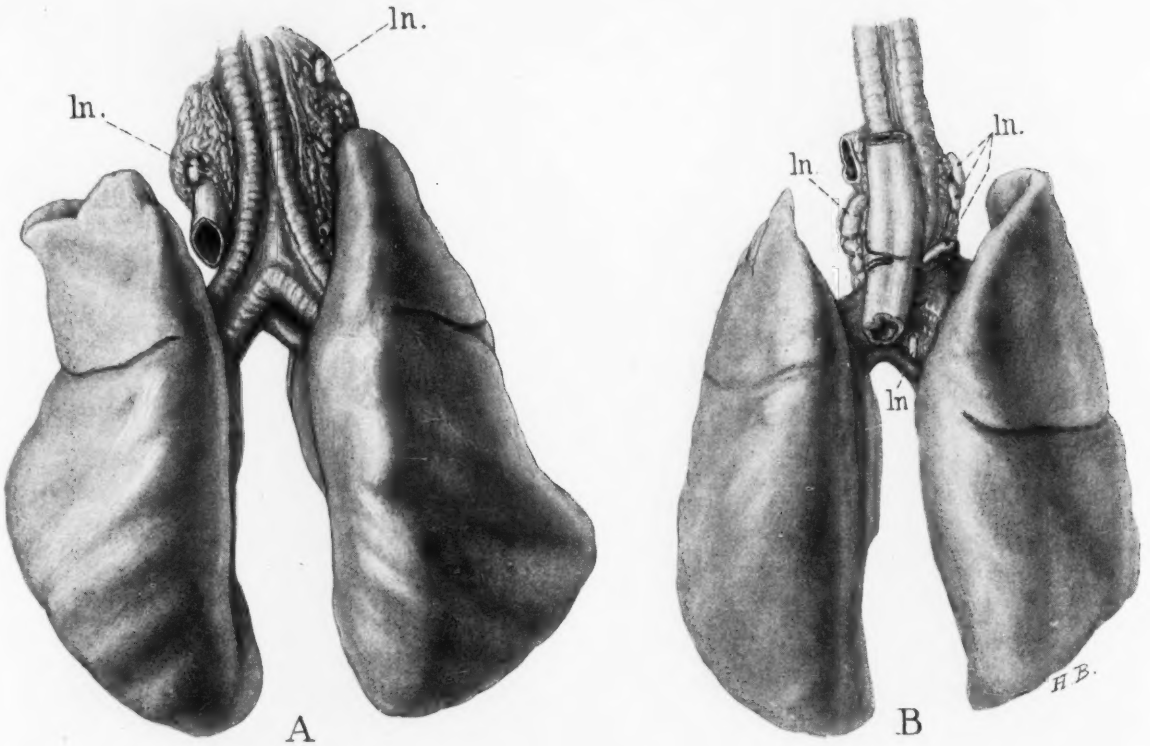

FIG. 1. DRAWING OF TWO RABBITS' LUNGS. × $\frac{7}{8}$

A: There are two lymph nodes, *ln.*, which lie on the surface of the mediastinal fat, one near the trachea on the left side, and the other near the ascending aorta.

B: In this animal the nodes are somewhat larger. The fat has been removed, so that the nodes lie nearer to the mediastinal structures than normally. There is a small lymph node at the bifurcation of the trachea, just dorsal to the pulmonary vein.

grayish or brownish bodies of quite soft and fat-like consistence. They occur more constantly and are larger on the right side, and lie, as a rule, 15 to 20 mm. cephalward from the bifurcation of the trachea, in or on a mass of mediastinal fat which holds them away from the trachea. The smaller nodes on the left side are frequently situated within the curve of

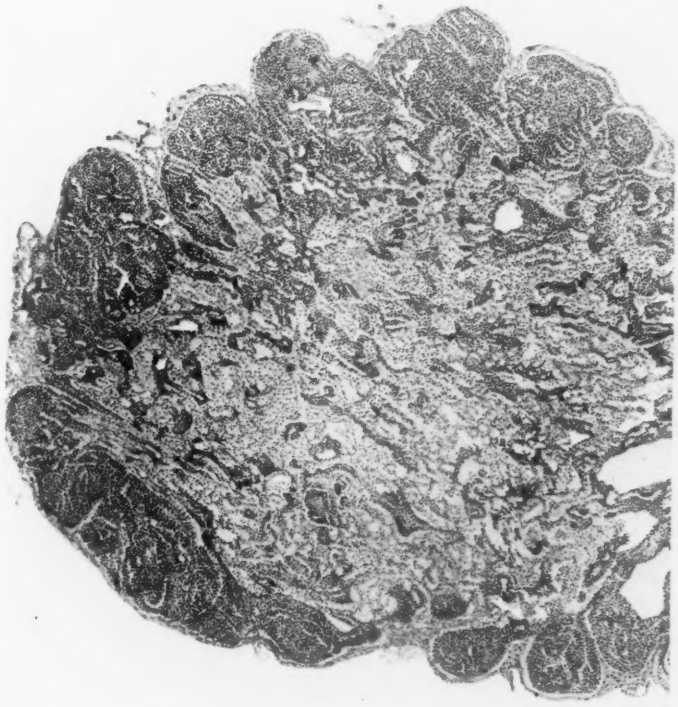

FIG. 2. RETOUCHED PHOTOMICROGRAPH OF HEMI-CROSS-SECTION OF TRACHEOBRONCHIAL LYMPH NODE OF RABBIT. × 30

The tissue of this lymph node is "open" with the cells relatively far apart. While these nodes are usually of this type, denser and more compact ones are also frequently seen.

the arch of the aorta; or they lie lateral or dorsal to the ascending aorta or the arch, or between these portions of the vessel and the trachea. Occasionally, a node may lie alongside the descending aorta at the level of the bifurcation of the trachea, and in rare instances a small node resides within the angle of the bifurcation itself.

Figure 1 illustrates these relations. Each drawing is from a normal

D. In this animal the nodes are somewhat larger. The fat has been removed, so that the nodes lie nearer to the mediastinal structures than normally. There is a small lymph node at the bifurcation of the trachea, just dorsal to the pulmonary vein.

rabbit's lung. In *A* the lymph nodes were partially embedded in the mediastinal fat, which is shown intact. In *B* the fat has been removed. It will be seen that the nodes vary in size and position in the two specimens. In *B* a small node lies within the angle of the bifurcation of the trachea.

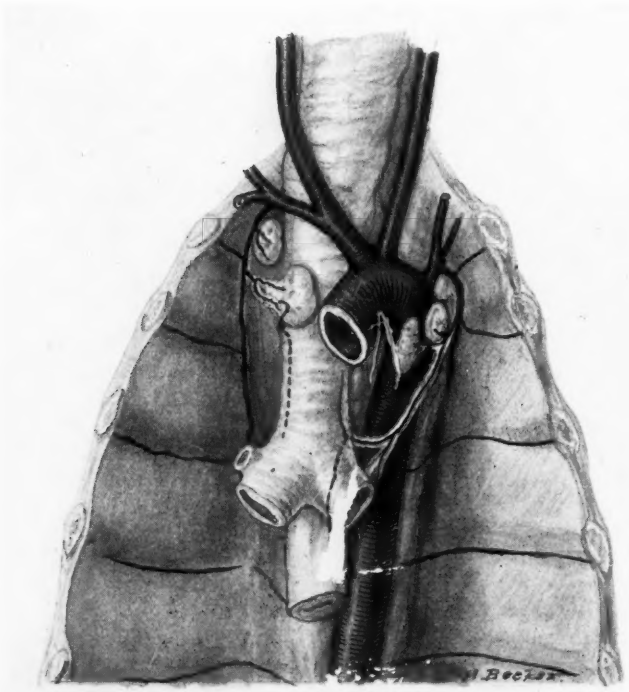

FIG. 3. DISSECTION OF INJECTED SPECIMEN. × 2

The lymph nodes derive their blood supply from twigs from a branch of the subclavian artery on either side. For further description see text.

Histologically, the appearance of these lymph nodes is rather characteristic. As may be noted in figure 2, the tissue is usually less dense, the individual lymphoid cells are further apart, with more and wider spaces between them, and the germ centres are smaller and more numerous than is usually the case with other lymphoid tissue in the rabbit. This appearance of "openness" accounts, no doubt, for the soft consistence of the nodes.

The technique of determining the blood supply of the nodes was as

follows: Under full anaesthesia and with the heart still beating, the abdominal aorta was exposed, and divided just proximal to the renal arteries. As soon as exsanguination had occurred, the sternum was split, and a ligature was tied around the aorta and pulmonary artery at the base of the heart. Through a cannula, inserted into the abdominal aorta, a suspension of lampblack[3] was now injected under pressure from a syringe. The abdominal aorta was then closed with a ligature, and the entire contents of the neck and thorax were removed *en bloc*, fixed in 80 per cent alcohol, and carefully dissected.

The vascularization of the rabbit's tracheobronchial nodes is uniform and constant. Deep within the thoracic cavity and very close to the vetebral column, a vessel arises from the subclavian artery on each side. It passes caudally, and, on its way, sends branches to the first four intercostal spaces, and, at the same time, three (sometimes only two) small branches to the tracheobronchial nodes and fatty tissue of the mediastinum as well. The last of these branches, after giving off a smaller branch to lymph nodes and fat, continues on, to supply the trachea and lower part of the oesophagus. The tracheal subdivision of this artery passes on to the bronchus and constitutes the bronchial artery. The small arteries on either side frequently anastomose with their fellows on the opposite side.

This vascularization is well shown in figure 3 which represents a dissected specimen. The trunk-vessel from the right subclavian artery, besides sending branches to the first three intercostal spaces, gives rise to two small vessels, which pass mediastinalward to the tracheobronchial lymph nodes, trachea and oesophagus. This trunk-vessel and its fellow on the left have their analogue in a somewhat similar vascular arrangement in the guinea pig, as described by Willis in *Study V* of this series (2). However, while the source of the trunk is also the subclavian, in the guinea pig from five to seven intercostal spaces are supplied by its branches, and the mediastinal structures all receive blood from a single, relatively large bronchial artery which arises from it on the right side.

Because of their more intimate anatomical relation with the trachea and their distance from the lung, as is observed frequently in the rabbit, one might ask whether these tracheobronchial lymph nodes lie in the

[3] Minute quantities of lampblack were gradually added to a few drops of water in a mortar, and ground into a thick paste. Twenty-five grams of lampblack were finally ground with enough water to make a paste, and then enough water was added to bring the total to one litre.

paths of drainage from only the trachea, large vessels and heart, rather than in those from the lungs. Such, it would seem, is not the case. Repeated attempts to reach the tracheobronchials by means of injections of the media and adventitia of the trachea have failed. On the other hand, when, in several animals, there was tuberculosis in the lungs, both right and left tracheobronchials were also tuberculous.

An additional and rather unrelated observation, as it arose in this study, may be mentioned here. The rabbit's thymus is quite large. It often extends nearly to the apex of the heart, and frequently contains small islands of lymphoid cells. It is supplied with blood by branches from the right and left internal mammary arteries.

SUMMARY

1. The tracheobronchial lymph nodes of the rabbit are very small, and relatively insignificant in view of the size of the rabbit's lung.

2. They are ordinarily disposed more along the trachea than around its bifurcation.

3. In about 20 per cent of the rabbits examined they were not visible. In such animals they may be microscopic.

4. Their blood supply is derived from branches coming from a trunk originating from the subclavian artery on either side. This trunk also sends branches to the first three or four intercostal spaces, as well as to the trachea and lower part of the oesophagus. The branch to the trachea continues on to the bronchus.

5. The thymus of the rabbit is extremely large.

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STUDIES ON TUBERCULOUS INFECTION[1]

XIV. THE LOCALIZATION OF TUBERCULOUS INFECTION IN THE RABBIT, WITH PARTICULAR REFERENCE TO THAT IN THE LUNGS

ALLEN K. KRAUSE

It may be recalled that *Study VI* of this series (1) was concerned with the relations, characteristic for the animal, of the lungs and tracheobronchial lymph nodes of the guinea pig to tuberculous infection. Until infection is rather advanced, it is typical for guinea pigs to exhibit more extensive tuberculosis in their tracheobronchial lymph nodes than in their lungs, by way of which and from which infection must have proceeded to the nodes, just as it is the usual event after infection to detect tuberculous changes in these regional lymph nodes earlier than they are visible in the lungs themselves.

The study involved a somewhat minute investigation of the paths and rate of spread of tuberculous infection in the guinea pig and of the factors responsible for the peculiarity of focalization mentioned. It disclosed that, after *first* infection, the dissemination of bacilli is extraordinarily rapid, and completes the circuit of the body within four days at the most, and no doubt earlier (see also *Study X* (2)). It could also show that for several weeks after infection (at least four weeks), infection of tracheobronchial lymph nodes was quantitatively greater than that of the lungs. Among other generalizations, it laid down that, *in the guinea pig*, while pulmonary infection and morbid change always contribute to those of the tracheobronchial lymph nodes, tuberculosis in the latter is the result and the reflection, not merely of tuberculosis in the lungs, but of tuberculosis anywhere in the body. And, since it is the guinea pig's spleen which is accustomed to show most tuberculosis early in the course of the infection, tracheobronchial-node tuberculosis will then be found ordinarily to run parallel with splenic tuberculosis and, quantitatively, to be dependent on the latter (or on that in any other extrapulmonary viscus).

[1] From the Kenneth Dows Fund for the Study of Tuberculosis, of the Johns Hopkins Hospital and University

At the time, broad differences between guinea pigs and rabbits, in respect to their response to experimental tuberculous infection, especially differences of focalization, were mentioned. These differences, and their probable explanation, constituted, in large part, the theme of the author's Harvey Society Lecture in 1922 (3), in which were communicated the general results, to date, of studies on tuberculous infection in the rabbit as well as in the guinea pig. The details of the investigations on the rabbit, which have remained unpublished, form the substance of the present study.

This will be devoted to the presentation, in the manner of an atlas, of the development of tuberculous infection within the rabbit's lung. Analysis of the data will follow in a *Discussion*, while their application to the problem of tuberculous infection in general will receive attention in a separate communication (*Study XV*).

FIGURES

Fig. 1. Tuberculosis of the rabbit's lung

When rabbits are infected experimentally, it is characteristic for the lungs to show tuberculosis first of all organs and, with the progress of the disease, to develop by far the most marked and extensive changes in the body. At the same time little, usually no, tuberculosis appears in the spleen.

Although the lungs thus seem to bear the brunt of the infection, a remarkable feature is the uniformly coincident relative freedom of the tracheobronchial lymph nodes from disease. The typical picture of rabbit tuberculosis, accordingly, is much involvement of the lungs with but little in the lymph nodes of the lungs.

Figure 1 brings out this relation strikingly. It illustrates the lungs of a rabbit which four months previously had received a *subcutaneous* inoculation of living bovine bacilli. The lungs are almost completely involved and "solid" with fibrocaseating tuberculosis, the development of which has doubled the size of the organs. It is difficult to imagine how an animal was able to live with so much pulmonary disease; yet it did not die naturally, but was killed.

To ensure a better examination of the tissues, the lungs and mediastinal contents were removed *en bloc* and fixed in formalin, and the dissection was then carried out on the hardened specimen. Nevertheless, so insignificant were the tracheobronchial lymph nodes that they were lost in the dissection.

The animal had no visible tuberculosis in either its spleen or liver; nor were the kidneys involved. Indeed, that of the lungs was the only noticeable disease in the body.

The illustration is natural size.

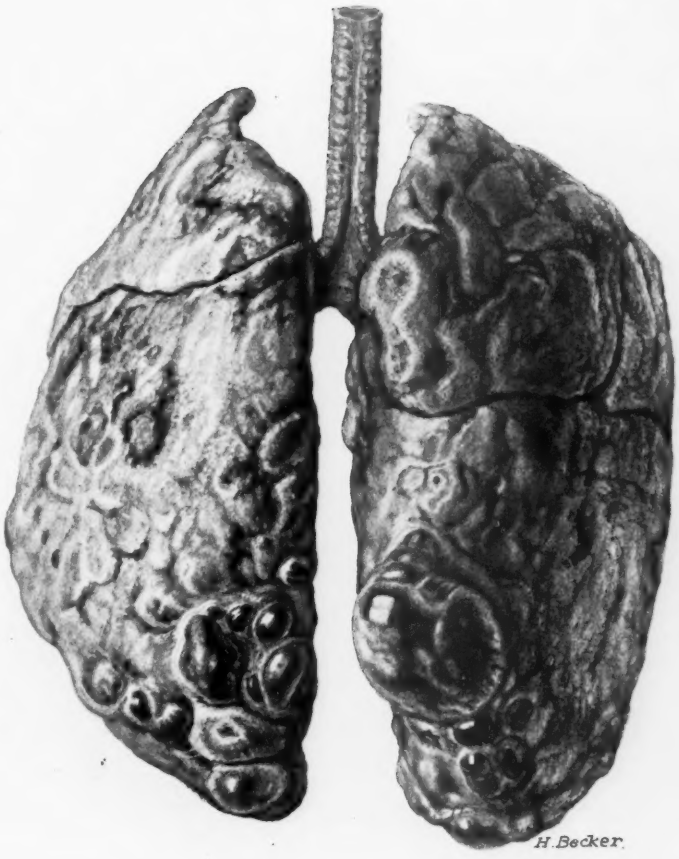


FIG. 1

Figs. 2, 3 and 4. The intrapulmonary lymphoid tissue of the rabbit

(Cf. fig. 5)

So far as is known, the lungs of all mammals normally contain aggregates of lymphoid tissue throughout the organ. As described by Miller (3) these collections are situated at definite locations, which, in summary, are

1: Where bronchi and bronchioles divide,

2: At points between the pulmonary artery (and its bronchus) and adjoining alveoli,

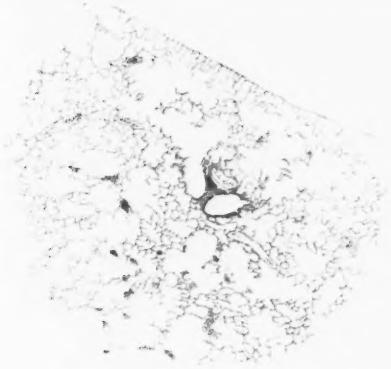
3: Where veins from the distal ends of the bronchioles join main trunks of the pulmonary vein, and

4: Where pleural venules join to form a pulmonary vein.

Under normal conditions this lymphoid tissue varies greatly in amount for different animal species. In rabbits it is very abundant and is particularly noticeable at the bifurcations of bronchi (bronchioles).

Figures 2, 3 and 4 present increasing magnifications of a mass of lymphoid tissue at the bifurcation of a bronchus out near the pleura in the lung of a normal rabbit. Tucked in between the dividing bronchus and the artery of the particular primary anatomical unit, its position is typical, as described by Miller. In figure 4 the lymphatics of the mass stand out plainly, and especially prominent is the one, of greatly elongated cross-section, situated between the lymphoid tissue and the artery.

The subpleural location of this lymphoid collection will emphasize that, normally, intrapulmonary lymphoid tissue is distributed out as far as the periphery of the rabbit's lung and is not merely confined to the larger trunks at the root of the lung.



Drawn by Dorothy Peters

FIG. 2

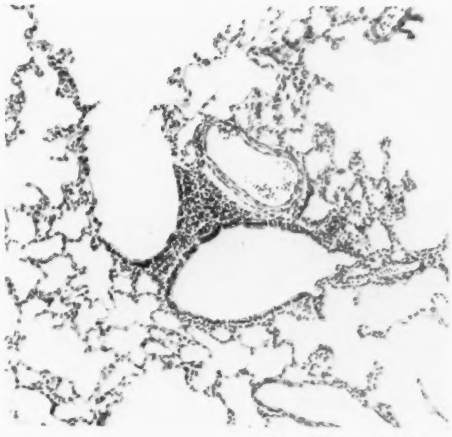


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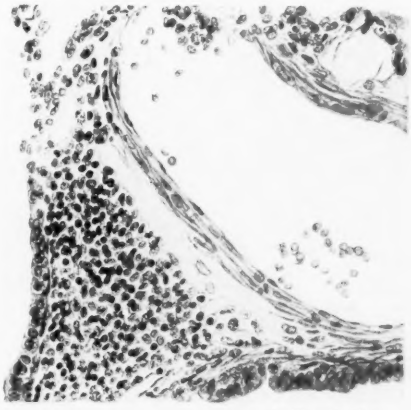
FIG. 3



Drawn by Dorothy Peters

FIG. 4

Fig. 5. The intrapulmonary lymphoid tissue of the rabbit

(Cf. figs. 2, 3, and 4)

This section of a normal rabbit's lung illustrates the abundance of intrapulmonary lymphoid tissue in the rabbit. The tissue is situated at points of branching of a bronchus, and three collections of it are to be seen on one slide. The characteristic location between dividing bronchus and pulmonary artery is again to be noted in the case of the uppermost and lowermost masses.

Since Willis, in *Study XIII* (4), has shown that the rabbit's tracheobronchial lymph nodes, that is, its extrapulmonary lymphoid tissue, are quite small, we may regard the rabbit as an animal, the lungs of which have much lymphoid tissue within them and relatively little of this tissue, in the way of regional lymph nodes, outside them. This relation is exactly opposite to that which obtains in guinea pigs, in which, as was pointed out in *Study VI* (1), normally tracheobronchial lymph nodes are large and intrapulmonary lymphoid tissue is scanty.

Drawn by Dorothy Peters

FIG. 5

Figs. 6 and 7. The localization of tubercle bacilli in the intrapulmonary lymphoid tissue of the rabbit immediately after infection

A rabbit was inoculated intracutaneously (ear-vein) with living tubercle bacilli, and killed *one hour* afterward.

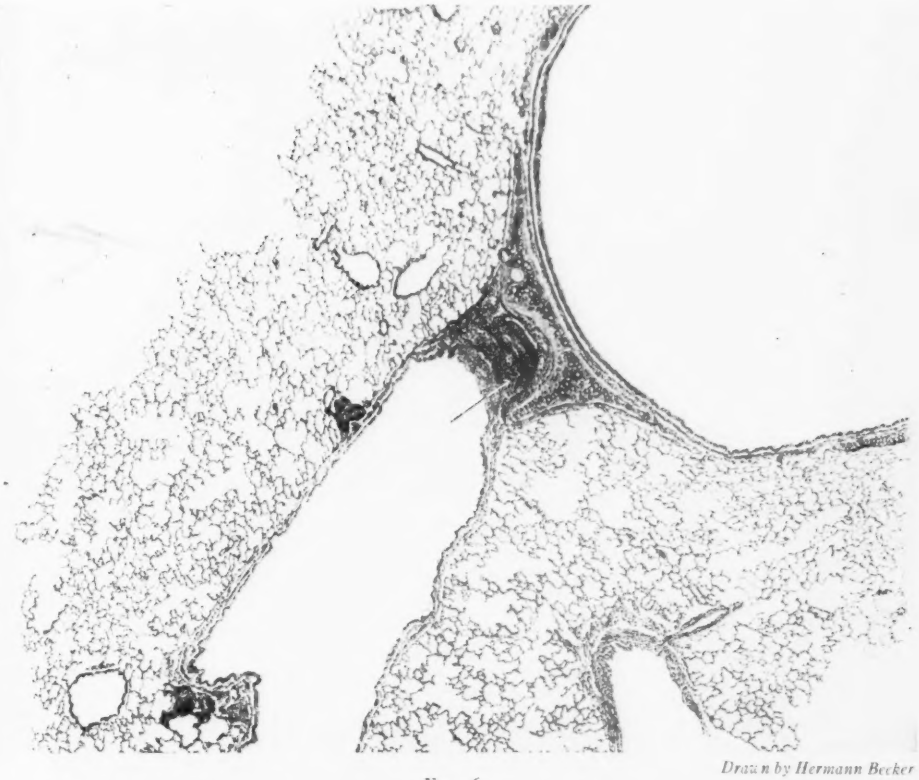
Figure 6 shows a section of its lung, which was fixed in distention with Zenker's fluid immediately after death, while the sections were stained with haematoxylin, orange-G and carbol-fuchsin (the latter subjected to acid-alcohol).

Since the animal was killed so soon after inoculation the section represents anatomical norms. In the proper situation, the bifurcation of a bronchus, is a large mass of lymphoid tissue, while at the lower left-hand corner, again at a point of branching, lies another mass of this tissue. The arrow, directed toward and into the large central collection, points to an intralymphoid blood-vessel, which is almost completely plugged with acid-fast bacilli.

This spot is shown in figure 7, a drawing of an oil-immersion image (x 720). Bacilli, introduced into the ear-vein and carried thence directly to the lung, have embolized at once in the lymphoid tissue. *Study IV* of this Series, by Miller (5), makes clear the reason for this localization. It will be recalled that Miller, investigating the vascular supply of the intrapulmonary lymphoid tissue of the rabbit's lung, found it to be derived from the *pulmonary artery*. Therefore, *in the rabbit*, bacteria that have gained the general venous system will, in part at least, be conveyed to this lymphoid tissue directly. The event depicted here is impressive biological proof of Miller's anatomical demonstration, and represents the prompt deposition in lymphoid tissue of inoculated bacilli brought to it by the pulmonary artery.

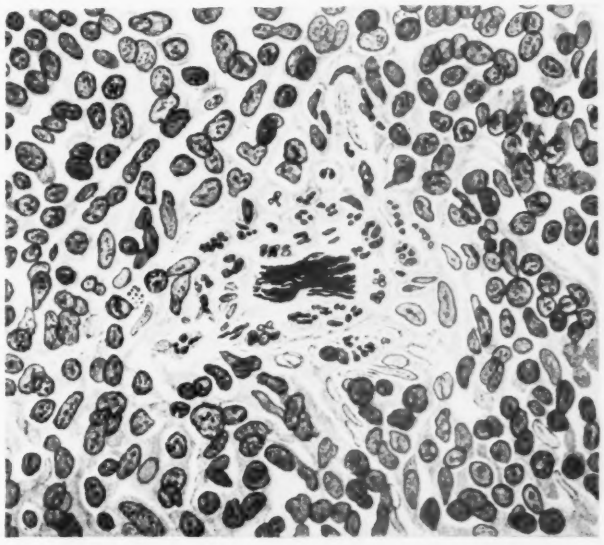
It may be repeated here that this altogether unexpected vascularization differs from that which prevails in the guinea pig. In the latter animal, as one would presume and as has been shown by Willis in *Study V* (6), the bronchial artery is the blood-vessel of supply to the intrapulmonary lymphoid tissue.

Although it has no bearing on the present study, the opportunity may be taken to call attention to the type of cellular reaction, depicted in figure 7 as the earliest response to large focalizations of tubercle bacilli. Here, only one hour after infection, and at presumably the same interval after localization of bacilli, polymorphonuclear leucocytes dominate the field, to the exclusion of all other cellular elements. Such a reaction may not be regarded as part of the specific cellular response to tuberculous infection. It always occurs promptly wherever large numbers of bacilli are deposited, and with a speed that varies directly with the mass of bacilli. It represents, in all likelihood, a nonspecific cellular response to aggregated protein. It soon disappears, as the more characteristic and specific cellular elements of tubercle come into view again, to reappear only when death and disintegration of tissue (tubercle) become prominent; in other words, again when products of protein are being set free in large amounts.



Drawn by Hermann Becker

FIG. 6



Drawn by Hermann Becker

FIG. 7

Figs. 6 and 7. The localization of tubercle bacilli in the intrapulmonary lymphoid tissue of the rabbit immediately after infection

A rabbit was inoculated intracutaneously (ear-vein) with living tubercle bacilli, and killed *one hour* afterward.

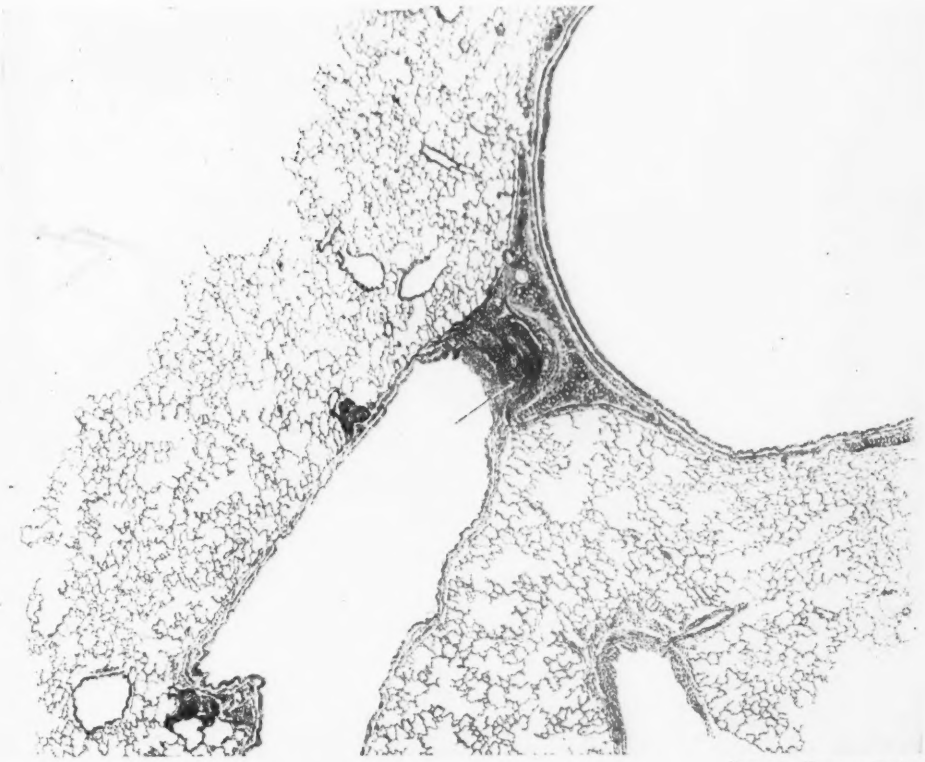
Figure 6 shows a section of its lung, which was fixed in distention with Zenker's fluid immediately after death, while the sections were stained with haematoxylin, orange-G and carbol-fuchsin (the latter subjected to acid-alcohol).

Since the animal was killed so soon after inoculation the section represents anatomical norms. In the proper situation, the bifurcation of a bronchus, is a large mass of lymphoid tissue, while at the lower left-hand corner, again at a point of branching, lies another mass of this tissue. The arrow, directed toward and into the large central collection, points to an intralymphoid blood-vessel, which is almost completely plugged with acid-fast bacilli.

This spot is shown in figure 7, a drawing of an oil-immersion image (x 720). Bacilli, introduced into the ear-vein and carried thence directly to the lung, have embolized at once in the lymphoid tissue. *Study IV* of this Series, by Miller (5), makes clear the reason for this localization. It will be recalled that Miller, investigating the vascular supply of the intrapulmonary lymphoid tissue of the rabbit's lung, found it to be derived from the *pulmonary artery*. Therefore, *in the rabbit*, bacteria that have gained the general venous system will, in part at least, be conveyed to this lymphoid tissue directly. The event depicted here is impressive biological proof of Miller's anatomical demonstration, and represents the prompt deposition in lymphoid tissue of inoculated bacilli brought to it by the pulmonary artery.

It may be repeated here that this altogether unexpected vascularization differs from that which prevails in the guinea pig. In the latter animal, as one would presume and as has been shown by Willis in *Study V* (6), the bronchial artery is the blood-vessel of supply to the intrapulmonary lymphoid tissue.

Although it has no bearing on the present study, the opportunity may be taken to call attention to the type of cellular reaction, depicted in figure 7 as the earliest response to large focalizations of tubercle bacilli. Here, only one hour after infection, and at presumably the same interval after localization of bacilli, polymorphonuclear leucocytes dominate the field, to the exclusion of all other cellular elements. Such a reaction may not be regarded as part of the specific cellular response to tuberculous infection. It always occurs promptly wherever large numbers of bacilli are deposited, and with a speed that varies directly with the mass of bacilli. It represents, in all likelihood, a nonspecific cellular response to aggregated protein. It soon disappears, as the more characteristic and specific cellular elements of tubercle come into view again, to reappear only when death and disintegration of tissue (tubercle) become prominent; in other words, again when products of protein are being set free in large amounts.



Drawn by Hermann Becker

FIG. 6

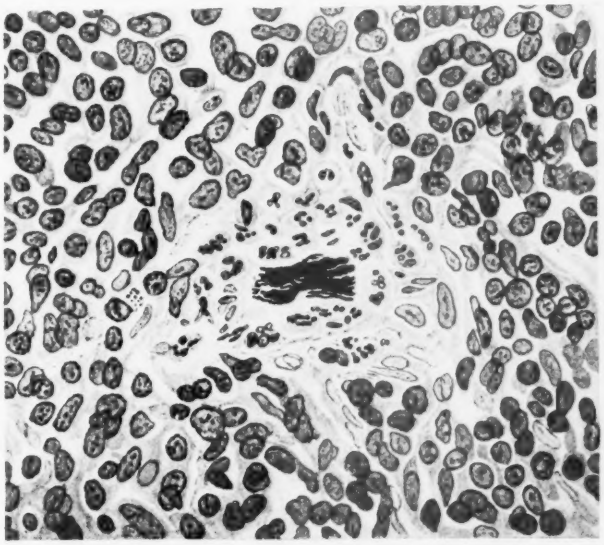


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FIG. 7

Fig. 8. The localization of tubercle bacilli in the intrapulmonary lymphoid tissue of the rabbit immediately after infection

(*Cf. figs. 9 and 10*)

A rabbit was inoculated intravenously (ear-vein) with living tubercle bacilli, and killed *four* hours afterward. The lungs were fixed in distention with Zenker's fluid, and sections were stained with carbol-fuchsin, decolorized with acid-alcohol, haematoxylin and orange-G.

Figure 8 therefore illustrates anatomical norms. There is a branching bronchus, with apparently a ring of lymphoid tissue at the point of division. There is also another mass of lymphoid tissue near the top of the specimen. The arrow points to a collection which will be shown at greater magnifications in figures 9 and 10.

The sections thus far shown will serve to bring out the great profusion of lymphoid tissue within the rabbit's lungs, the importance of which, as a probable factor in the characteristic focalization of tubercle in the rabbit, will be elaborated later.

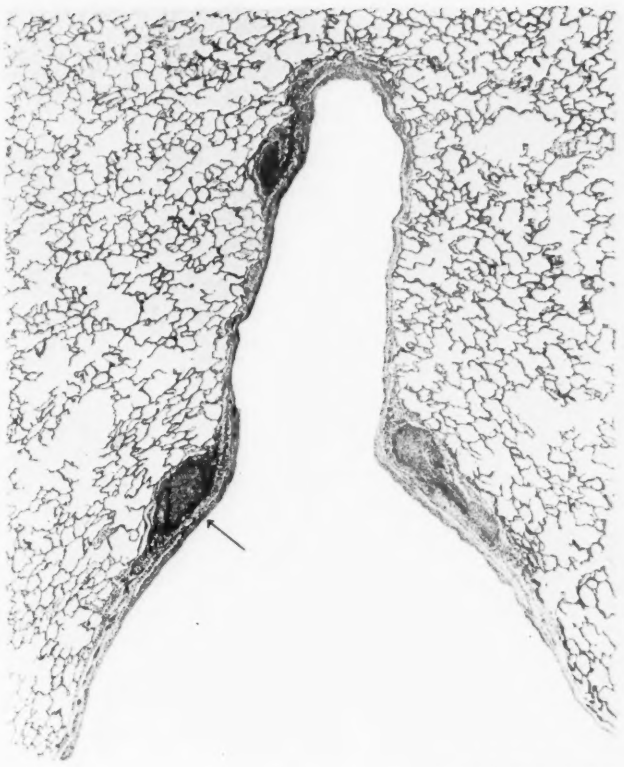

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FIG. 8

Figs. 9 and 10. The localization of tubercle bacilli in the intrapulmonary tissue of the rabbit immediately after infection

(Cf. fig. 8)

Figure 9 shows an enlargement of the lymphoid mass designated by the arrow in figure 8. Two clumps of acid-fast bacilli are to be seen within a blood-vessel traversing the lymphoid tissue.

These are brought out in greater detail in figure 10, a drawing of an oil-immersion field (x 1000). The central blood-vessel encloses two large clumps of tubercle bacilli and two smaller ones. At the lower right-hand corner is also a small collection of five bacilli within another blood-vessel. The polymorphonuclear reaction is evident, although not nearly as pronounced as in the specimen from the rabbit killed one hour after inoculation.

The two specimens of early focalization, one hour and four hours, respectively, after infection, are direct visible and tangible evidence in support of an hypothesis that in the rabbit (and other animals, as well) the minute structure of an organ set in the normal path of transportation of microörganisms (infection) is a determinant of where infection shall "take hold" and develop.

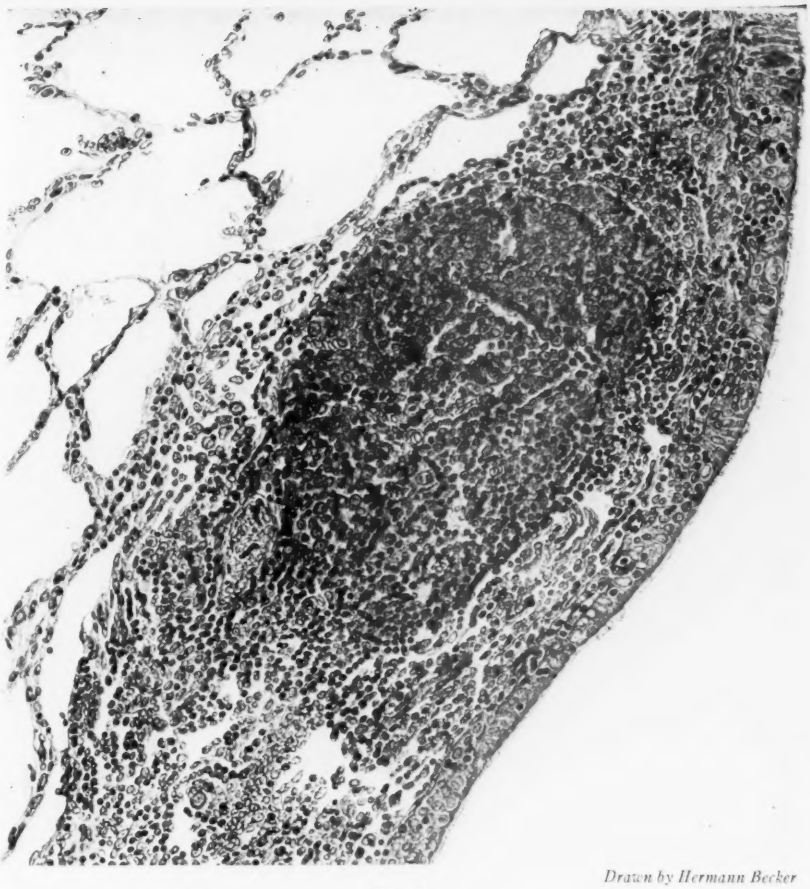

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FIG. 9

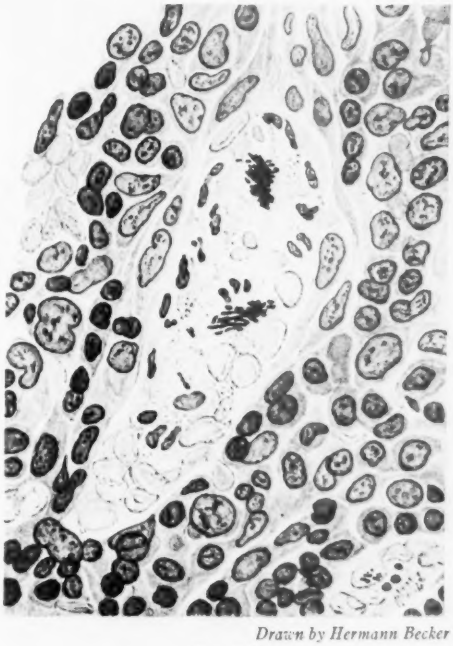

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FIG. 10

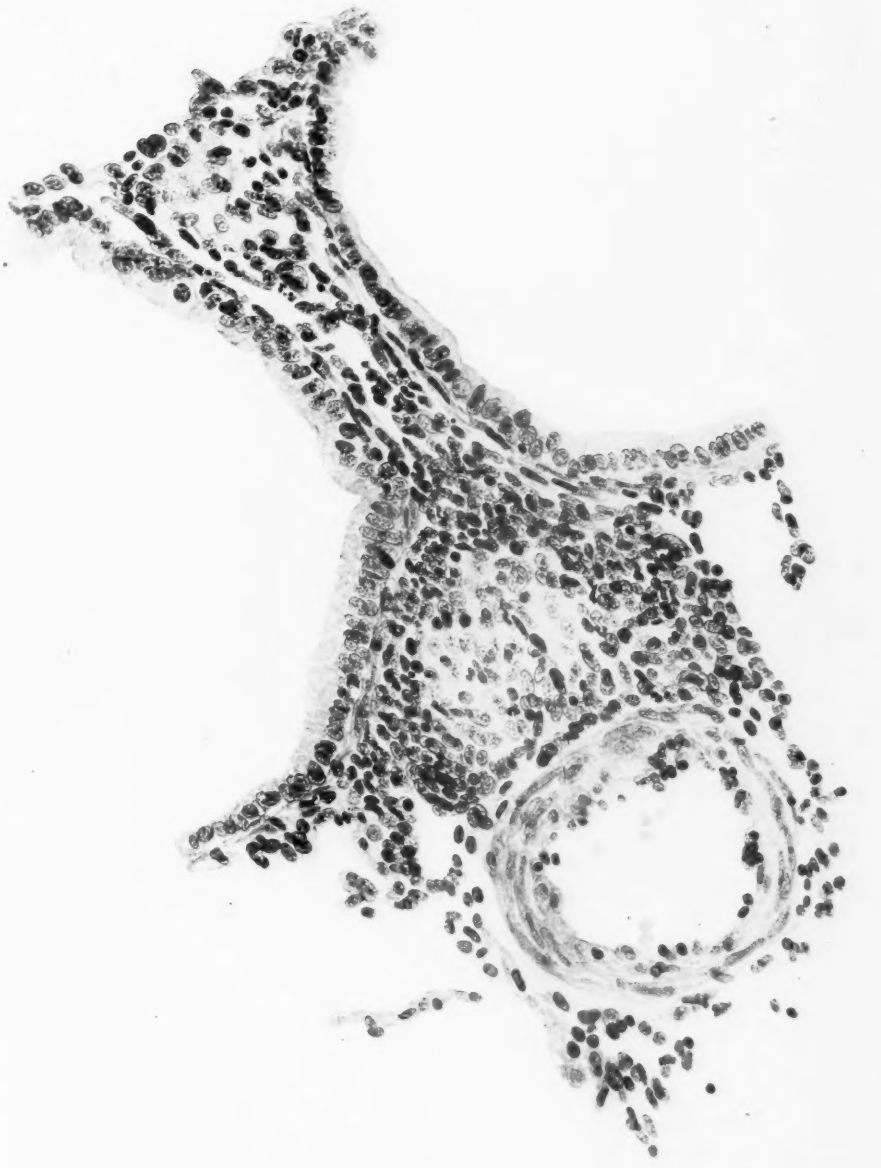
Fig. 11. The focalization of infection as found later in the rabbit's lung

A rabbit received an intravenous (ear-vein) inoculation of living tubercle bacilli, and was killed *twelve days* later. Sections of the lungs were stained with haematoxylin and eosin.

Figure 11 is representative of the findings in this animal. So soon after inoculation, changes in the lungs are likely to be scanty and slight; but when they did appear here they were most noticeable in the lymphoid tissue of the bronchi.

In the section illustrated the lymphoid tissue is in its characteristic situation, at the point of division of a bronchus, and between the latter and its artery (pulmonary). From here, also, it extends into the crotch of the branching air-passage.

There is typical early tubercle, just beginning to degenerate and caseate, most noticeable in the centre of the main mass of lymphoid tissue, with also a focus in the extension of the tissue at the upper edge of the section.



Drawn by Dorothy Peters

FIG. 11

Fig. 12. The focalization of infection as found later in the rabbit's lung

(Cf. figs. 13, 14, 15, 16 and 17)

A rabbit was inoculated intravenously (ear-vein) with living tubercle bacilli, and killed *twenty-five days* afterward. Sections from the lungs were stained with haematoxylin and eosin.

The illustration, shown in figure 12, is a drawing of a hemi-cross section of this rabbit's lung. The original was made in color, on a scale of about thirty-times enlargement, so that the drawing measured thirty inches in its long diameter at the base. This was then photographed, when it was brought down to a diameter of nine inches, and the photograph was retouched. The figure has been made from this photograph.

The purpose of the illustration was to bring out the topography of pulmonary focalization of infection after intravenous inoculation, at a time (twenty-five days) after infection, when most of the significant depots of primary focalization could reasonably be presumed to have become evident, and not too much secondary extension have developed to obscure or confuse the original sites of deposition of bacilli.

The illustration shows beautifully and decisively the preponderant rôle played by intrapulmonary collections of lymphoid tissue as receiving stations of tubercle bacilli, and perhaps also as "intercepters" of bacilli that may be moving hilumward with the lymphatic flow. A short distance back of the pleura is a last peripheral zone of larger bronchioles, such as are opposite points *1*, *2*, *3* and *4*, with their accompanying branches of the pulmonary artery. Here, this single section shows most collections of lymphoid tissue between the bronchioles and arteries to be involved with tubercle. At the base is a large main bronchus, which has just divided, one branch of which is indicated by *5*. In the crotch of the bifurcation is lymphoid tissue (see also fig. 15), the lighter half of which is plainly tuberculous. Another large mass of lymphoid tissue, which "caps" the bronchus to the right, is also tuberculous for the most part.

Indeed, throughout the section it is evident that infection, coming to the lungs by the blood, has plainly localized in lymphoid tissue, usually that in association with bronchi; or it is probable that, in the few instances in which this relation of foci is not so clear, serial sections would disclose it at another plane of the tissue. It may also be significant that, as we proceed from the periphery to the base of the section, we find that the extent of the separate foci increases.

Drawn by Dorothy Peters

FIG. 12

Figs. 13 and 14. The focalization of infection as found later in the rabbit's lung

(Detail of area 2 of fig. 12)

Figure 13 represents a detail drawing at greater magnification of the area designated *2* in figure 12. Figure 14 is a drawing of the same formation, as it appears in another section (serial), cut at a more distal plane. Figure 13 illustrates the structure proximal to the point of branching of the bronchus. Figure 14 shows the bronchus just dividing. We therefore view sections from two levels of the same process, twenty-five days after intravenous inoculation.

The lymphoid mass, set in the angle of the bifurcating bronchus, and between this and the pulmonary artery, is tuberculous and is beginning to caseate. As one would expect, the process is more extensive at the centre of the mass (figure 14) than toward its periphery (figure 13).

We get here, also, a beautiful picture of how tubercle extends lymphatically. From the central lymphoid tissue it is creeping out, no doubt by way of the lymphatic vessels, which are particularly prominent between the lymphoid tissue and the adjacent pulmonary artery (see figures 4 and 11), so that, as appears in figure 14, it is now completely encircling the artery. It will likely continue to spread by the lymphatics of the artery's adventitia, and, with time, stretch out into the surrounding tissue by lymphatic connections, while detached and mobilized bacilli will proceed toward the hilum by lymphatics. Encroachment upon the encircled artery will set up conditions that promote thrombosis, normally so prominent a feature in the "outriding zone" of an extending tuberculosis.

At higher magnifications, the areas *1*, *3* and *4* of figure 12 showed, on serial sections, features identical to those noted in figures 13 and 14.

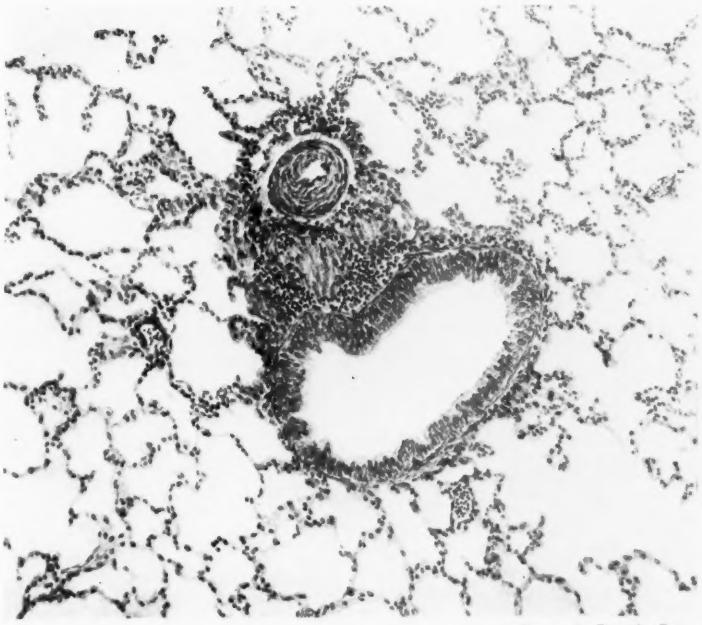


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FIG. 13

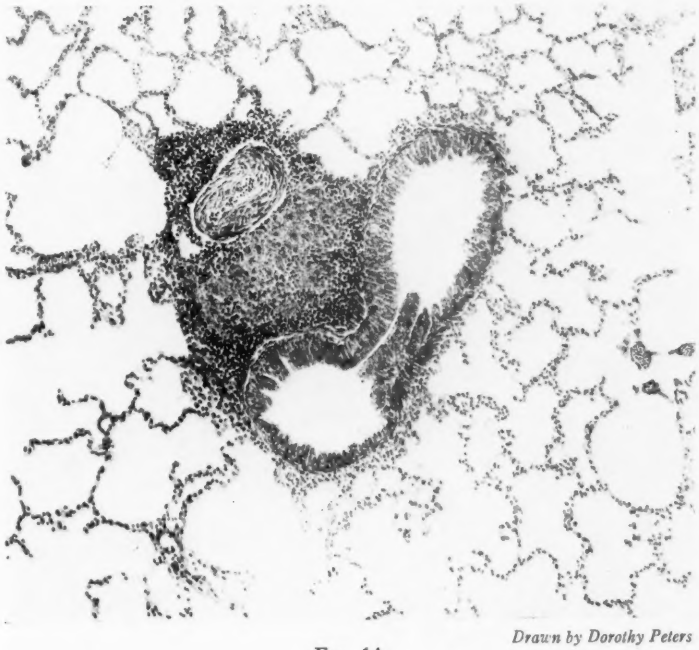

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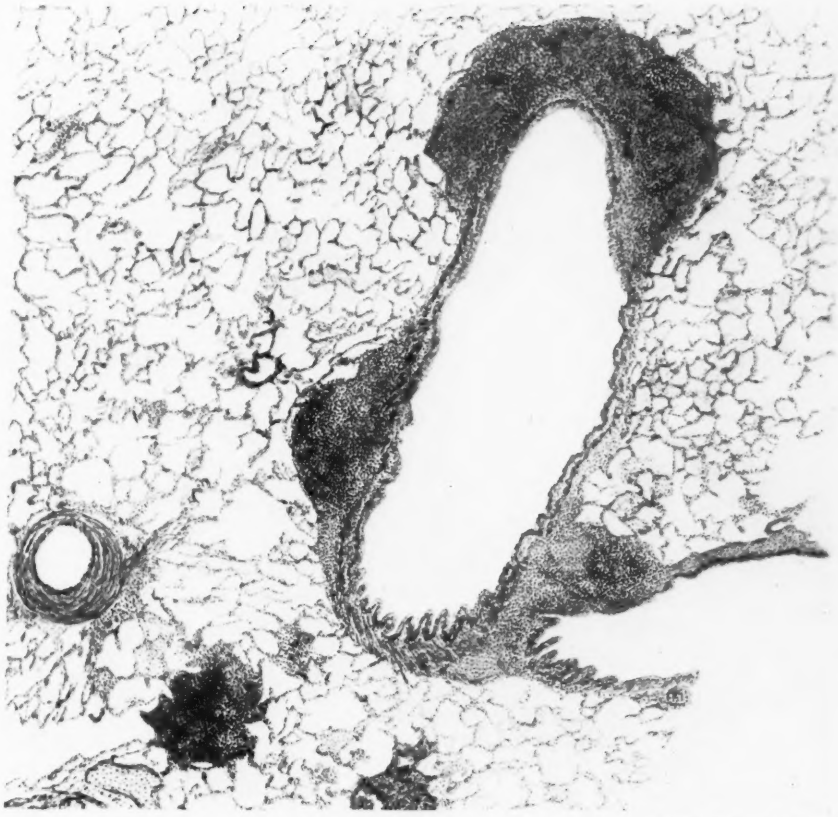
FIG. 14

Fig. 15. The focalization of infection as found later in the rabbit's lung

(Detail of area 5 of fig. 12)

This enlargement of area 5 of figure 12 brings out more clearly the tuberculous changes that are under way in all masses of lymphoid tissue associated with a large bronchus just after its bifurcation near the root of the lung. The process, it may be repeated, is part of an infection twenty-five days after inoculation of the ear-vein.

Detail drawings of the lymphoid tissue in the angle of the dividing bronchus and of that "capping" the bronchus at the top appear in figures 16 and 17.



Drawn by Dorothy Peters

FIG. 15

Figs. 16 and 17. The focalization of infection as found later in the rabbit's lung

(Details of fig. 15)

Figures 16 and 17 bring out clearly the tuberculous nature of the process in the lymphoid tissue of the bronchus shown in figure 15. The tissue at the top of the bronchus (figure 17) is almost completely involved, and is occupied by far the most extensive focus depicted in the whole hemi-section of the lung (figure 12). At the same time, the left half of the lymphoid mass in the angle of the bifurcation (figure 16) is almost entirely replaced by tubercle, while the right half remains more intact.

Caseation has, as yet, hardly become evident in either area. The tuberculous changes in each are made up of typical epithelioid cells, the outlines and nuclei of which are still clean-cut and distinct. In this respect, these particular foci, near the root of the lung, do not appear to be quite as old as those near the periphery (figure 14) in which caseation is pronounced. But, one would not wish to push the point too far.

Drawn by Dorothy Peters

FIG. 16

Drawn by Dorothy Peters

FIG. 17

DISCUSSION

It is plain, from the foregoing demonstration of the development of tubercle after experimental intravenous infection, that its intrapulmonary lymphoid tissue must have much to do with the characteristic tendency of the rabbit's lung to tuberculous infection. Immediately after infection (one hour) we find bacilli set down within this tissue, as they have been brought to it directly by the pulmonary artery. As early as twelve days after infection it is the most noticeably involved of all intrapulmonary structures, and at twenty-five days after infection its position in this respect is still more prominent,—so much so, indeed, that almost all tubercle at this time seems to be focalized in it.

It is well understood by experienced students of tuberculous infection that one determinant of the places where bacilli will focalize and tubercle will develop, and of the sequence of this focalization and development, is the original portal of entry of the bacilli and the avenues which they may take in their later dissemination. Inhaled tubercle bacilli may arrive at tracheobronchial lymph nodes in a child, and there set up morbid change, which, erupting later, may sow the lungs and, for the time being, only the lungs, with tuberculous pneumonia. Ingested tubercle bacilli may, via natural paths, come to rest in the retroperitoneal lymph nodes, from which a sufficient eruption of caseous foci provides the setting for generalized miliary tuberculosis.

In the rabbit the significant thing is that, *no matter how tubercle bacilli are introduced into the body,* if disease progresses and spreads from its first localization at or near a portal of entry, and as it progresses, it is to the lungs to which it goes and it is in the lungs where all or most of it appears. This is not the ordinary event for all animals, as has so frequently been mentioned in these *Studies*; in the guinea pig, for instance, the lungs are relatively spared and, if we may speak of such a thing as a "seat" or "organ of predilection," this is the spleen.

Since the systemic venous system converges in the pulmonary artery, and thus in the lungs, we would expect intravenous inoculation to eventuate in pulmonary tuberculosis predominantly; or, conceivably, even to the exclusion of disease elsewhere. That is, we would expect this if all organs of the body were alike in their capacity to receive and to retain tubercle bacilli. The focalization of infection would then be merely a matter of bacilli moving, fortuitously or otherwise, along certain natural channels of dissemination and of coming to rest where dynamic factors

promoted cessation of progression, while the extent of foci and the vigor of their development would, in large degree, depend upon the numbers of bacilli brought to an organ and the frequency of their reception.

But we have seen, as in figure 1 which is representative of what occurs in the rabbit, that subcutaneous inoculation of this animal is also wont to result in most tuberculosis in the lungs, and frequently, as happened in the case illustrated, in all visible visceral tuberculosis in the lungs.

When we search for an explanation of this peculiarity and "specialization" of localization we naturally turn to the intrapulmonary lymphoid tissue as soon as we learn that there is such a thing in mammals and that it exists in rabbits in great quantity. Miller's discovery of a vascular supply to this tissue by the pulmonary artery strengthens the probability that we are on the right track; for, ordinarily, we would presume that the bronchial artery supplies these lymphoid collections in all animals, just as Willis has found to be the case in the guinea pig. The fact of a pulmonary-artery vascularization in the rabbit of itself vastly increases the chances of the tissue becoming infected, as will be obvious. When, now, we show that immediately after infection it is not particularly difficult to find deposited in the blood-vessels of this tissue bacilli that have been brought to it by the pulmonary artery, we are beginning to make probabilities certain by factual evidence.

Yet all this will not explain why, with the early evolution of pulmonary infection in the rabbit, the lymphoid tissue displays so much infection and the other structural elements of the lung so little. The branching pulmonary artery goes to all the countless septa designed for gaseous exchange, and the number of points where bacilli brought by it may come to rest and settle in the lung can be limited only by the number of the artery's ultimate divisions. Why, therefore, do we not see early foci distributed more indifferently throughout the lung? Why are such a large proportion in relation with the lymphatic tissue? Why do not bacilli lodge everywhere, and everywhere set up tubercle?

The fact is that, at first, bacilli do lodge everywhere and, immediately after intravenous infection, may be found in the smaller blood-vessels of all the finer structures of the lung. We have many times inoculated human and bovine tubercle bacilli and timothy bacilli, and have easily discovered them at many points, including the alveolar walls, from a few minutes to several days after inoculation.

Foci will frequently arise at these points of localization outside lymphoid tissue, and such foci are to be seen in every lung in animals similarly

treated. But the fact of importance and significance is that, early in infection and while tubercle is discrete, the lymphoid tissue is most prominently affected. Although tubercle bacilli are brought to the lungs by the blood in these experiments and are first fixed in the lungs as emboli in blood-vessels, it is only very rarely that tubercle formation takes place in the lumina of blood-vessels. The bacilli, after coming to rest, are carried out of the lumina. They are thus brought within the province of the lymphatic system. If they begin their pulmonary career as emboli in the blood-vessels of the lymphoid tissue, they, no doubt, set up foci in the surrounding lymphoid cells. But if they are first distributed in other tissues, we may believe that in many instances, perhaps as a rule, they are soon carried into lymphatic vessels and moved along with the lymph. They are now in a system that is beset everywhere with innumerable collections of cells, lymphoid aggregations, which would serve to obstruct further passage to the hilum. It is generally accepted that a major function of lymphatic tissue (lymph nodes) is to receive foreign particles and arrest their progress. The process is often spoken of as one of "filtration." We would not be so precise in our ideas of the mechanism concerned,—we can imagine other possibilities than a screen-like barrier,—but we consider it beyond question that lymph nodes, lymph follicles, lymphoid collections, act everywhere as intercepters and arresters of bacteria.

Accordingly, intrapulmonary lymphoid tissue receives, not only those bacilli that are brought to it by the pulmonary artery, but all the bacilli that make their way to the innumerable lymphoid masses by the lymphatics from every part of the lung. Soon or late, all bacilli, which are picked up anywhere by "phagocytic" cells and carried to lymphatics, arrive at a mass of lymphoid tissue. They may be fixed there, or they may go through and on to the next proximal collection of cells,—and so on. If lymphoid tissue within the lung is scanty and if lymphatic flow is unimpaired and active, the general tendency will be for the bacilli to be carried completely through the lung and out of it—to the "draining" lymph nodes of the lung. But if lymphoid tissue is in great abundance or if lymphatic channels become blocked and the flow of the lymph impeded, conditions are at hand to keep the bacilli, with consequent tubercle formation, within the lung.

In the rabbit we have all these latter conditions fulfilled, in addition to a vascularization which would carry many bacilli directly to the lymphatic system within the lung. In a certain sense, we may regard the

rabbit's lung as one that is "closed" lymphatically. Therefore, much tuberculosis within the rabbit's lung; therefore, also, but little tuberculosis in its tracheobronchial lymph nodes or at other points outside the lung. Any widespread distribution of tuberculosis in the rabbit calls for the breaking of a focus into a systemic artery and a dissemination thereby, an event that would be rather extraordinary.

It is probably significant that figure 12 shows more extensive foci as one goes from the periphery toward the hilum. This feature would suggest a convergence of infection toward the root as bacilli keep, for a time at least, moving centripetalward from many points more peripheralward. Again significant may be the appearance of more recent pathological change in the more extensive central foci of figures 16 and 17 than in the peripheral focus of figure 14. Because of its situation the latter must be practically the result of an original focalization of bacilli; the lymphoid tissue, in which it is situated, can have but a limited drainage area. But the drainage area of the lymphoid tissue of figures 16 and 17 is conceivably the greater part of the lung; so that we would expect increments of infection to have been coming to it continually during the period since inoculation.

The illustrations bring out one more point that may be instructive. Prettier "peribronchial" tuberculosis than that depicted in figure 15 can hardly be imagined. It is not improbable that more than one pathologist upon viewing a similar arrangement and disposition of foci in sections cut from autopsy material has been impressed by how much support they have given to a bronchogenous (inhalation or aspiration) origin of the particular foci. For, if bronchogenic tubercle is not to be found in the immediate neighborhood of bronchi, where is one to look for it?

Yet in this case we know that the foci arose haematogenously; for, under controlled conditions we introduced the bacilli by the ear-vein. Indeed, in these animals of haematogenous infection most of the early tuberculosis is seen, in one way or another, to be related topographically to the air-passages.

SUMMARY

1. In the rabbit the lungs are normally the organs most affected with tuberculosis after experimental inoculation of every kind.

2. In this respect the rabbit differs from some other animal species, as, for instance, the guinea pig.

3. Within one hour after intravenous infection tubercle bacilli are found in intrapulmonary lymphoid tissue.

4. During the first four weeks after intravenous infection tubercle is most prominent in the intrapulmonary lymphoid tissue, especially that which is in association with bronchi (bronchioles).

5. The determinants of this peculiarity of localization are structural (anatomical) norms, some of which are more or less peculiar to the rabbit.

6. Most decisive are the quantity of intrapulmonary lymphoid tissue and its blood supply.

7. In the rabbit this tissue is supplied by the pulmonary artery.

8. The tissue is very abundant.

9. The contribution of these two factors ensures direct infection of the lymphoid tissue by blood-borne bacilli, and the intrapulmonary fixation of bacilli that are being moved lymphatically through the lung.

10. A peribronchial disposition of tubercle is, of itself, no assurance of its bronchogenic origin.

11. In the rabbit, most foci are found to be in relation with bronchi during the first few weeks after intravenous infection.

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STUDIES ON TUBERCULOUS INFECTION[1]

XV. SUMMARY, ANALYSIS AND APPLICATIONS OF THE STUDIES ON TUBERCULOUS INFECTION

ALLEN K. KRAUSE

This series of *Studies* was undertaken primarily to gather accurate data toward the solution of two main problems. We wished to put beyond conjecture, if possible, certain opinions that a correlation of various observations had led us to entertain. We had long been impressed by the fact that the characteristic focalization of tuberculosis in the guinea pig differed from that in the rabbit, a circumstance that recalled a familiar analogue in human beings, in whom discrete pulmonary tuberculosis typically tends to be more prominent at the root of the lung in childhood, and out in the lung or toward its periphery in later life. We had reason to believe that a common factor might be responsible for the difference in both instances, and that this might be demonstrable in the smaller laboratory animals. At the same time, we had arrived at certain ideas of the mechanism of tuberculo-immunity, which we desired to put to the test of experiment.

The two problems took shape as follows:

1. Does the lymphatic system play a decisive part in the focalization of tuberculous infection, especially pulmonary infection? If so, what are its significant elements?

2. How does tuberculo-immunity arrive at its effects, that is, less and more chronic disease; and through what agencies does it work?

THE RÔLE OF THE LYMPHATIC SYSTEM IN THE PULMONARY FOCALIZATION OF TUBERCULOSIS

The frequently mentioned pulmonary results of single virulent *subcutaneous* tuberculous infection of guinea pigs and rabbits are well portrayed in plate 1. Here are presented for purposes of comparison the lungs and

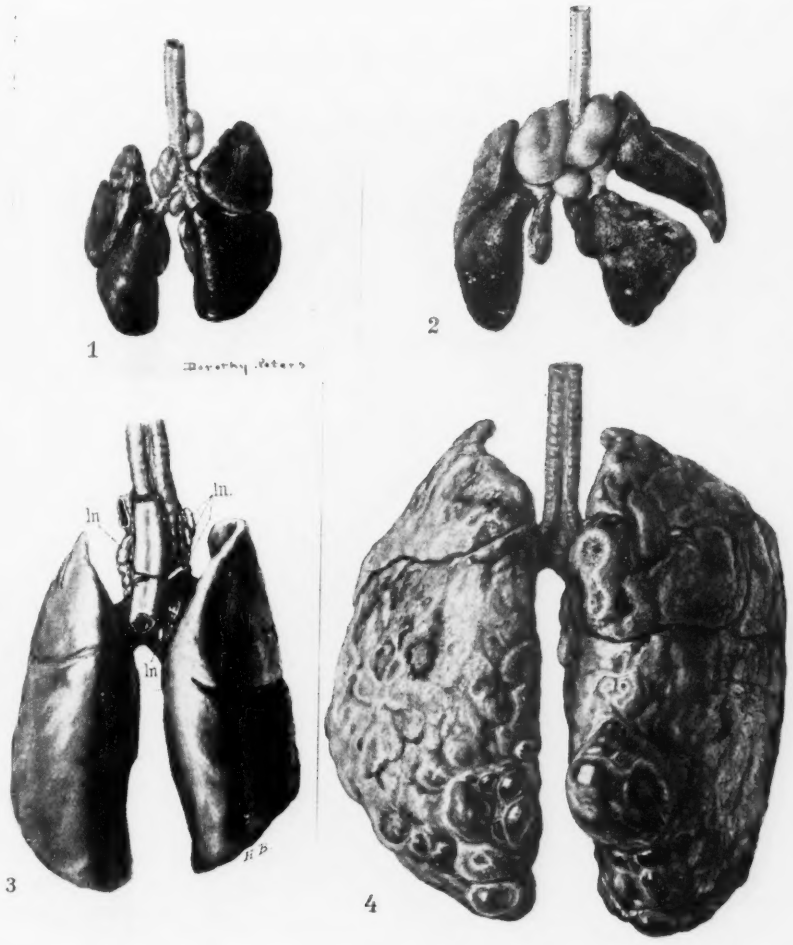
[1] From the Kenneth Dows Fund for the Study of Tuberculosis, of the Johns Hopkins Hospital and University.

tracheobronchial lymph nodes of both nontuberculous and tuberculous animals. The drawings represent characteristic findings. Figure 1 displays the normal guinea pig's lungs, with their relatively extensive equipment of extrapulmonary lymphoid tissue, that is, tracheobronchial lymph nodes. It may be contrasted with figure 3, in which are shown the lungs of the normal rabbit, much larger, yet scantily supplied with tracheobronchials. When guinea pigs become tuberculous, then, as depicted in figure 2, the tendency is for manifest pulmonary disease to appear but sparsely and accumulate slowly, as the tracheobronchials undergo a more extensive involvement. Under the same conditions of infection the situation in the rabbit, as appears in figure 4, is exactly reversed; for its lungs become extremely infected, as, meanwhile, its tracheobronchials, if they exist, have little or no tuberculosis.

Meanwhile, marked and contrasting differences of localization of infection are to be observed elsewhere in the two animals. In the guinea pig, the spleen is the most common and the earliest internal organ to be involved, and will, for a considerable time, exhibit the most extensive disease; in the rabbit the spleen is rarely affected with visible tuberculosis. Showing first foci later than the spleen, the guinea pig's liver is a frequent seat of manifest tubercle, and, until later in the course of the disease, keeps well ahead of the lungs. Ordinarily, little or no tuberculosis is to be seen in the rabbit's liver.

These, as well as other characteristic differences of tuberculous infection in the two animals, are described in detail in *Study VI*, to which the interested reader is referred. They have long been recognized and commented upon, and, remaining unexplained satisfactorily, seemed to offer a promising field for investigation.

In the routine study of experimental tuberculosis we had, as early as 1910, become impressed with an obvious, and indeed striking normal histological feature of rabbit's lungs which was not noticeable in the lungs of guinea pigs. In the former there were always numerous aggregations of what appeared to be lymphoid tissue; in the latter these entered so little into the general picture as to attract no attention until intentional search for them was made. It was then found that guinea pigs also possessed, normally, intrapulmonary lymphoid tissue, but in amounts so small as to be insignificant when compared with the rabbit. The literature of *Tuberculosis* was searched to no effect for allusions to this tissue, particularly as to whether it might be concerned in experi-



NORMAL AND TUBERCULOUS LUNGS AND TRACHEOBRONCHIAL LYMPH NODES OF GUINEA PIG AND RABBIT COMPARED

(For description see text)

Fig. 1. Guinea pig, normal. The tracheobronchial lymph nodes are large, while intrapulmonary lymphoid tissue (*cf.* text) is scanty. (See also *Study VI.*)

Fig. 2. Guinea pig, tuberculous, after subcutaneous inoculation. The typical result; with but little intrapulmonary tuberculosis and prominent involvement of the tracheobronchials. (See also *Study VI.*)

Fig. 3. Rabbit, normal. The tracheobronchial lymph nodes are invisible or small, intrapulmonary lymphoid tissue is in great abundance. (See also *Studies XIII* and *XIV.*)

Fig. 4. Rabbit, tuberculous, after subcutaneous inoculation. The characteristic result, with marked tuberculosis of lungs, and little or no noticeable involvement of the tracheobronchials. In this instance, despite great care, the tracheobronchials were lost in the dissection. (See also *Study XIV.*)

mental tuberculosis. It was only when, in 1916, a fortuitous acquaintance was made with William Snow Miller's anatomical specimens of lungs of varied types and animals, that the possibilities of the case presented themselves; and suggested that systematically planned studies, with attention concentrated on the lymphatic apparatus, might shed some light on several habitually puzzling features of tuberculous infection, and particularly pulmonary infection. At the time Miller had already published *The Distribution of Lymphoid Tissue in the Lung.* A purely anatomical study, and not attempting or pretending to enlarge upon any pathological or etiological implications, it had appeared in *The Anatomical Record* (1911), and had apparently for this reason been overlooked by pathologists. But to the worker in tuberculosis, especially to one whose curiosity and interest in intrapulmonary lymphoid tissue had already been aroused, it could not help being enormously suggestive, with such scattered *obliter dicta* as

I have followed through serial sections numerous small miliary tubercles situated in the parenchyma of the lung; in every instance I have been able to trace their origin to one of the situations in which I have described lymphoid tissue as being present in the normal lung.

I cannot recognize the lymph follicles and lymph nodes described by him [that is, by Lüders] and other investigators, in the pleura, as normal structures; they must be pathological and must have developed from the normal masses of lymphoid tissue. This development may arise from the presence of irritating substances as, for example, particles of carbon. In this case we find more or less pigmentation of the masses of lymphoid tissue and deposition of pigment along the course of the lymph vessels throughout the lung.

Scattered aggregations of pigment are present in the lymphoid tissue. . . . . The increased amount of lymphoid tissue is undoubtedly due to the presence of irritating particles of carbon.

I am forced to believe that in the lungs . . . . the quantity of lymphoid tissue increases from childhood to old age and that this increase is largely due to the irritation arising from the constant irritation of irritating substances.

With the contrasted histomorphology of rabbit's and guinea pig's lungs before us, and now fortified by Miller's observations, there at once came to mind the possibility that tuberculosis was wont to be pronounced in rabbit's lungs because bacilli, in their deposition in the lung and their

further passage through it, were intercepted and held by innumerable masses of this intrapulmonary lymphoid tissue; and that normal guinea pigs' lungs tended to escape much involvement because the passage of bacilli through them was relatively unimpeded. In general, the first pronounced obstruction to pulmonary transit in the guinea pig would normally be encountered at places at or near the hilum.

This tentative hypothesis of relatively free and open pathways of pulmonary infection in the guinea pig was strengthened by a prolonged series of observations on the outcome of infection of guinea pigs with tubercle bacilli of low virulence. These observations form the basis of our *Study I.* Years of experience with a germ of constantly low virulence (strain R1) had taught us that, after subcutaneous inoculation, it would not provoke visible tubercle in internal viscera,—spleen, lungs, etc. We became accustomed to look for effects only near the site of inoculation,—in inguinal, and perhaps iliac lymph nodes; and had come to believe that the guinea pig's defense, capable of resisting slightly virulent microörganisms, had, at such more peripheral points, put a stop to the progress of the infection. However, in animals allowed to live for a long time the tracheobronchial lymph nodes would also be involved in the infection. We therefore had, as an end-result, tuberculosis of peripheral lymph nodes, such as the inguinals, and of central lymph nodes, the tracheobronchials, with all organs situated along the intervening channels of dissemination spared. Inasmuch as, to arrive at the tracheobronchials, practically all bacilli had first to come to the lungs and traverse these, it was necessary to imagine an intrapulmonary set of conditions which hampered the focalization of bacilli there and promoted their passage to the still more central tracheobronchials. The idea of an "open" lung, lymphatically, in the guinea pig gained in probability, and appeared to be pertinent to a much-disputed side of human pulmonary tuberculosis, in that, under certain circumstances, there *could*, and presumably *did*, exist tracheobronchial tuberculosis, even marked on occasion, without visible pulmonary tubercle. Pulmonary *infection* had, of course, to antedate tracheobronchial *infection;* but *manifest* tracheobronchial changes needed no accompanying manifest pulmonary focus.

It had now become necessary, by more direct and sufficient evidence, to establish more firmly the hypothesis of an "open" lung for the guinea pig; and to discover more exactly and completely the relations which

tracheobronchial infection might bear to tuberculosis elsewhere in the guinea pig. There arose for experimental inquiry such questions as: How soon after infection at a remote point (for instance, the groin) do tubercle bacilli, moving lymphatically and venously, reach the lungs and tracheobronchials? Proceeding then by systemic arteries, how quickly are they distributed generally throughout the body? Is, indeed, the tendency after first infection toward strict circumscription (as has been taught), or is it toward generalized distribution from the very beginning? Early in infection, while normal structural relations are unimpaired, do lungs or do tracheobronchials receive most of those bacilli that come to the respiratory system? The dependence of tuberculosis of the tracheobronchials on pulmonary infection and foci is assumed and granted; but is tracheobronchial tuberculosis to be weighed only as being accessory to pulmonary infection? Is it possible that tracheobronchial tuberculosis, its extent and its severity, may be dependent upon tuberculosis elsewhere than in the lungs?

All of the foregoing queries received consideration and, we believe, answer in *Study VI*. After first infection of nonimmunes the distribution of tubercle bacilli to all parts of the body is astonishingly rapid and complete. Within a very few days germs reach and settle out in spleen, lungs and tracheobronchial nodes. Their arrival at the two last-named places must be regarded as being virtually coincident (although, in point of actual time, appearance of germs in lungs must precede that in tracheobronchial lymph nodes). The technical methods employed to estimate quantitative relations suggested that during the first few weeks after infection bacilli are more numerous in tracheobronchial nodes than in the lungs of the same animal; the commonly observed event of a more extensive process in the tracheobronchials soon after infection (see fig. 2) pointed to the same circumstance. The contingency of tracheobronchial infection and disease is not restricted to intrapulmonary events, much though these must always influence it. The tracheobronchials, in developing tuberculosis, will "reflect" tuberculosis, and respond to it, in organs and tissues other than the lungs; to tuberculosis, perhaps, at any place in the body. Since the guinea pig's spleen, of all organs, commonly suffers most tuberculosis, a correlation of tracheobronchial tuberculosis, in respect to extent, can most frequently be made with disease in the spleen.

Confirmation of many of the chief findings of *Study VI*, and some of its conclusions as well, are to be found in the observations and protocols of

other workers, who have since published investigations of various phases of tuberculosis. In our *Study X* Willis reported that there is an almost immediate transportation of tubercle bacilli from the site of inoculation in nonimmunes, even when infection has been performed intracutaneously and with relatively small "doses." When Webb, Ryder and Olcott infected guinea pigs subcutaneously, they observed so thoroughly generalized a dissemination of bacilli as to set up tuberculosis of the mesenteric lymph nodes (as well as others in no way directly connected with the portal of entry or a central viscus). Our *Study VI* gave us reason to regard tuberculous *infection*, in general (including human tuberculosis), as being quite likely far more diffused, or "constitutional" from a topographical point of view, than has usually been taught to be the case. Ideas on this subject have been, more or less, "by-products" of this series of studies. They need not be enlarged upon here; and may be found *in extenso* in a paper, *The Spread of Tuberculous Infection in the Body* (1924), in which the attempt is made to show how a correlation of authenticated experimental, clinical and epidemiological data rather favors the hypothesis that tuberculosis, not unlike syphilis, is a disease of numerous loci of infection, yet with few manifest foci of anatomical changes.

Webb, Ryder and Olcott's experiments are very important to any fundamental conceptions of tuberculosis. They themselves realized the still greater importance of discovering whether these numerous minimal foci of slight metastasis were likely to remain always quiescent or to heal. They could not convince themselves that they did heal, although it is doubtful whether they kept their animals long enough to decide this point. To all intents and purposes the mesenteric-node foci remained inactive; and the authors stated, "It is apparent however that these lesions do not tend to progress, as does tuberculosis of the regional nodes adjoining the area of primary inoculation." It was our *Study VII*, which inquired into the conditions that influenced tuberculosis of the lymph nodes in general, and laid down that "The progression or retrogression of tubercle in this animal's [guinea pig's] lymph nodes is largely dependent on the progression or retrogression of the peripheral foci;" that is, those peripheral foci, "drainage" from which usually originates tuberculosis of lymph nodes regional to them. We would presume, from all our work, that rarely, unless influenced by some direct environmental force, will lymph-node tuberculosis progress if a sufficient transmission of bacilli from peripheral points to it is not kept up.

Observations culled from the notes of Rogers and of Baldwin and Gardner, both of whom conducted *inhalation* experiments on guinea pigs, are in harmony with the idea of an "open" lung in these animals. Rogers had his guinea pigs inhale moist sprays of tubercle bacilli. Autopsies seven days afterward, at a time when tubercle became visible for the first time in the lungs, disclosed distinct enlargement of the tracheobronchials. Baldwin and Gardner report instances in which, soon after guinea pigs had inhaled tuberculous sprays, noticeable involvement of the tracheobronchials preceded that of the lungs, and they tabulate an R1 animal (inhalation infection), whose tracheobronchials were positive and whose lungs were negative for tubercle bacilli.

Because they were unexpected, such observations are all the more confirmatory of our general hypothesis. One could hardly predict that much could be learned about whether bacilli tended to pass through, rather than remain in the guinea pig's lung, by the use of a technique that involved the inhalation of bacilli. Inhalation will concentrate too many bacilli, in large masses, upon the pulmonary tissues, and will, of course, lead to more tuberculosis in the lung than in any other place (such as the spleen); at least, it will do this for a while, just as will subcutaneous inoculation at the site of entry. To study delicate quantitative differences, we must resort to some method, such as subcutaneous inoculation, which will "feed" bacilli to the lung in moderate quantities.

Further on in the same study, Baldwin and Gardner give an admirably worked-out account of the microscopic evolution of tuberculous infection in the guinea pig's lung after inhalation. It seems that the regular event is for the first "crop" of tubercles to appear immediately beneath the pleura, and that, "shortly after the subpleural tubercles have reached the height of the degenerative stage . . . . there appears a second generation of lesions in the depth of the lung, usually in the outer half." These latter tubercles are abortive, a consequence, no doubt, of the tissue allergy occasioned by the first tubercles.

It would seem that the time of their appearance, as well as their allergic character, stamps these later tubercles, situated centralward to the first ones, as the resultant of bacilli that have been mobilized from more peripheral points and carried root-ward through a lung in which passage is naturally free. But with time has come an opposing force, namely, allergy, which operates to fix bacilli, and thus to a certain extent nullify the normally easy and unimpeded transit through the lung. All such observations will be seen to be of great significance when we come to a consideration of the factors at work in immunity.

As for other findings presented in our *Study VI* Baldwin and Gardner confirm, by subcutaneous inoculation, "the regular progression of lesion through the lymphatic system and spleen," as there brought out. They state how, with numbers of bacilli "so small, it is possible to study the sequence of the reaction [that is, the allergic reaction of later metastasis] step by step," a point emphasized by us three paragraphs above as pertinent to any inquiry into the paths of infection. After *subcutaneous* inoculation of extremely dilute (for this purpose) suspensions of R1, they find so rapid a dissemination of bacilli that five days later the lungs of six out of a total of seven guinea pigs were proved by animal inoculation to contain bacilli.

The general proposition of relative involvement of the several organs and tissues, and of the relation of tracheobronchial tuberculosis to that in organs other than the lungs, as worked out in *Study VI*, was later confirmed from Corper's laboratory in a study by Rensch and Moore. Their findings are the more valuable because they sought to discover whether the same sequence and association of events holds good when varied and quite small "doses" of bacilli are used. After inoculations (subcutaneous) that ranged from 0.1 to 0.000,000,1 mgm. bacillli, they reported their observations as being "entirely in accord with the findings recorded by Krause."

It would appear therefore that on the evidence of biological experiment the hypothesis of an "open" lung, leading to little intrapulmonary and pronounced tracheobronchial involvement in guinea pigs, was well grounded. We now asked whether anatomical evidence would support this inference; and whether the hypothesis would withstand the crucial test of our modifying the capacity of the guinea pig's lung to escape infection; that is, by artificially altering those structural relations which we had postulated as being responsible for a relative freedom from pulmonary tubercle. But, before summarizing and analyzing this part of our work, it might be well to make perfectly clear what is meant by conditions designated as "little extrapulmonary and pronounced tracheobronchial involvement," "relative freedom from pulmonary tubercle," etc.

The reader must not get the idea that ordinarily guinea pigs will not develop pulmonary tuberculosis, or that they cannot or do not contract a great deal of tuberculosis within the lung. We have already intimated

that, if made to inhale most sprays of tubercle bacilli, they very promptly exhibit pulmonary tubercle, which may rapidly come to involve the lungs pretty thoroughly. We can also arrive at the same result by sending large numbers of tubercle bacilli directly to the lungs by way of the veins (intravenous inoculation). Such results are simply accomplished by concentrating at one time quantities of bacilli so massive that, even though there existed quite competent channels to carry particles out of the lung, and on to its lymph nodes, these avenues would soon become "choked up," as it were, and obstructed by their "overload." and an excess of bacilli would be left in the lung to set up extensive infection. However, even then, as has been brought out above, there may be carried to the tracheobronchials enough bacilli to cause changes that become visible there coincidently with or a very short time before any appear in the lungs.

It is when we introduce bacilli in a way to ensure a procession and succession of moderate numbers along the natural avenues of dissemination that we can gain an accurate and satisfactory idea of the comparative capacity of each tissue to receive and retain bacilli. Then only can we regularly observe the step-like sequence of first appearance of foci in the several parts of the body, and the later development of these foci. It is then also that we find, during the first part of the infection, that in the spleen more tubercle arises than in any other organ, and that the lungs are but slightly affected while the tracheobronchial lymph nodes are definitely to markedly involved. Later, as manifest disease continues to progress, and extend throughout the body, mobilized bacilli,—all those which have attained the venous system,—will be continually coming to the lungs. By reason of this accretion of infection, as well as through the extension of older intrapulmonary foci, the lung may, later, come to have a great deal of tuberculosis. But this will be at a time when new determinants of focalization will have been operating; such as allergy tending to fix bacilli *in situ*, and lymphatic flow made abnormal and less active by tubercle at the root and, little by little, reacting upon more central channels within the lung.

When, now, we examined the structure of the guinea pig's lung for elements that may conceivably influence intrapulmonary lymphatic flow, we found, indeed, those features which bespeak unobstructed passage and unusually active flow of lymph. The reader will find the anatomy of the lymphatic apparatus of the lung described in Miller's

Study III of this series; and we assume that the general account there given holds good for the guinea pig. As concerns intrapulmonary lymphoid tissue, a quantitatively variable component in different mammals, we have already stated that it is, under normal conditions, relatively scanty in guinea pigs. As would be expected, and as was definitely determined in our *Study V* by Willis, its source of blood supply

FIG. 5. REPRODUCED FROM OUR STUDY V, BY WILLIS, TO SHOW THE RICH LYMPHATIC SUPPLY AND EXCEPTIONALLY HEAVY MUSCULATURE OF THE GUINEA PIG'S LUNG

A: Pulmonary artery. *B:* Anastomosing trunk. *C:* Bronchial artery. *D:* Bronchus. The lymphatics in the wall of the pulmonary artery are numerous and large. The musculature of the media of both pulmonary artery and bronchus is very heavy, and has here narrowed down the lumen of the artery and thrown up the bronchial mucosa into deep rugae,—both appearances quite characteristic of microscopic sections of normal guinea pigs' lungs. (See text.)

is the bronchial artery. Therefore, particles (bacteria) coming directly to it by the blood should be only that small fraction of all arterially borne particles which are of the bronchial artery's share.

In order to make plainer several peculiarities of pulmonary structure of the guinea pig, which may bear some relation to the lymphatic flow within the lung, there are reproduced herewith, as figure 5 and 6, two

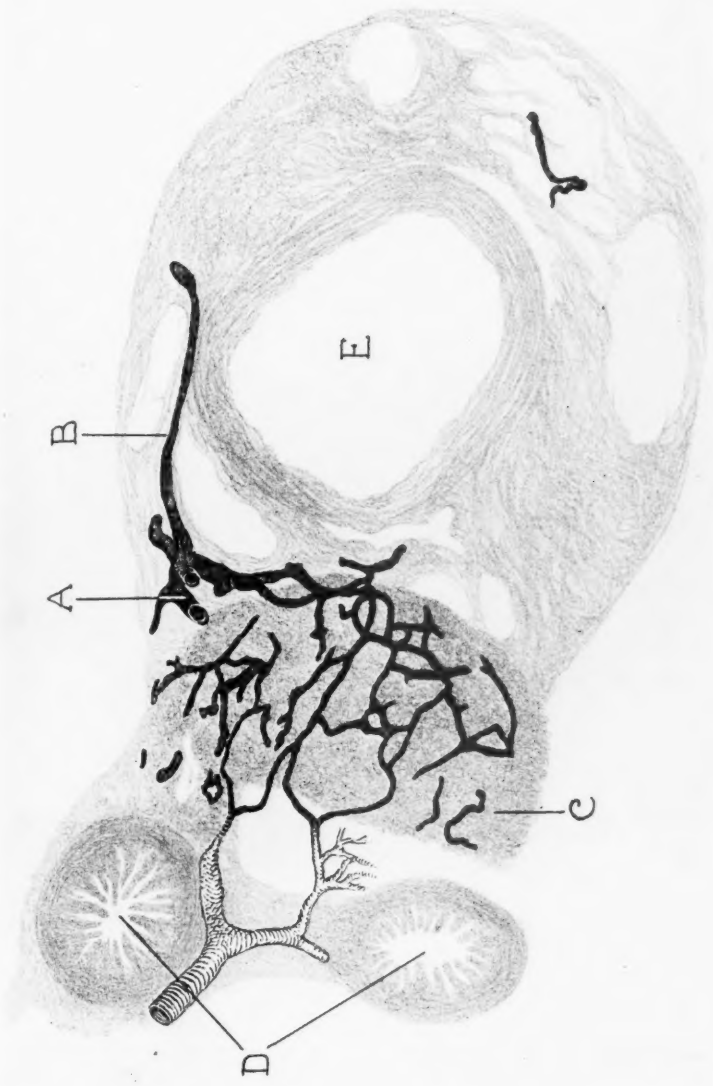


FIG. 6. REPRODUCED FROM OUR STUDY V, BY WILLIS, ALSO TO SHOW THE RICH LYMPHATIC SUPPLY AND THE HEAVY MUSCULATURE OF THE GUINEA PIG'S LUNG

A: Bronchial artery. *B:* Branch of injected bronchial artery, coursing as a vas vasorum of the pulmonary artery, and breaking up to supply intrapulmonary lymphoid tissue, *C*. *D:* Bronchi. *E:* Pulmonary artery.

The illustration brings out still better the features to which attention was called in figure 5. (See text.)

illustrations which originally appeared as figures 2 and 4 of our *Study V* by Willis. In figure 6 we see the bronchial-artery branch penetrating the mass of lymphoid tissue lying between the dividing bronchi and pulmonary artery, to break up into a capillary network in the tissue. This makes plain the tissue's blood-supply. But especially noteworthy in both figures is the rich supply of lymphatic vessels, most of which are here coursing along the adventitia of the pulmonary artery. Besides being abundant, they are large and their lumina are wide-open. Significant also is the extraordinarily heavy musculature of the tissues of the lung; indeed, it is doubtful whether any other mammal can exhibit an intrapulmonary musculature that will compare with the guinea pig's. In the drawings the bronchial mucosa is thrown up into exaggerated *rugae*, which greatly narrow the lumina, and the musculature of the media of the pulmonary artery is hardly less prominent than that of the bronchi.

So exceptional a musculature, normally present in so small an animal as the guinea pig, must, of course, have its purpose. To be correlated with it, quite likely, is the fact that of all animals the guinea pig manifests uniformly and most markedly the spastic respiratory features (not unlike fulminant bronchial asthma) of anaphylactic shock. We find, also, that so great are the activity and irritability of this bronchial musculature that the most gentle attempts to distend the lungs completely by intratracheal injections of fluid or air frequently fail, even with the lungs removed from the body, because whole lobes or large portions of them go into spasm, as the bronchi clamp down and prevent the entrance of the injection medium.

We must believe that such an arrangement makes for unusual mobility of the guinea pig's intrapulmonary structures during life, as the lung responds to all its accustomed stimuli. Lymphatics, coursing in the walls of bronchi and blood-vessels, and just outside their musculature, must, of course, be affected by excessive muscular activity. We know that muscular activity is a prime factor in motivating lymph flow, wherever it can exert an influence on the latter. We would presume,

FIG. 7. SECTION OF LUNG, TO SHOW RICH LYMPHATIC SUPPLY AND SMALL AMOUNT OF LYMPHOID TISSUE IN THE GUINEA PIG

The enormous and wide-open lymphatics are the striking feature of this section, and give one an idea of the freedom of lymphatic flow in the lung of the guinea pig. At the same time the lymphoid tissue is slight in amount, even though the location is at the bifurcation of larger bronchi. (*Cf.* figures 2, 3, 4, 5 and 8 of *Study XIV* and figures 8 and 9 of this *Study*.)

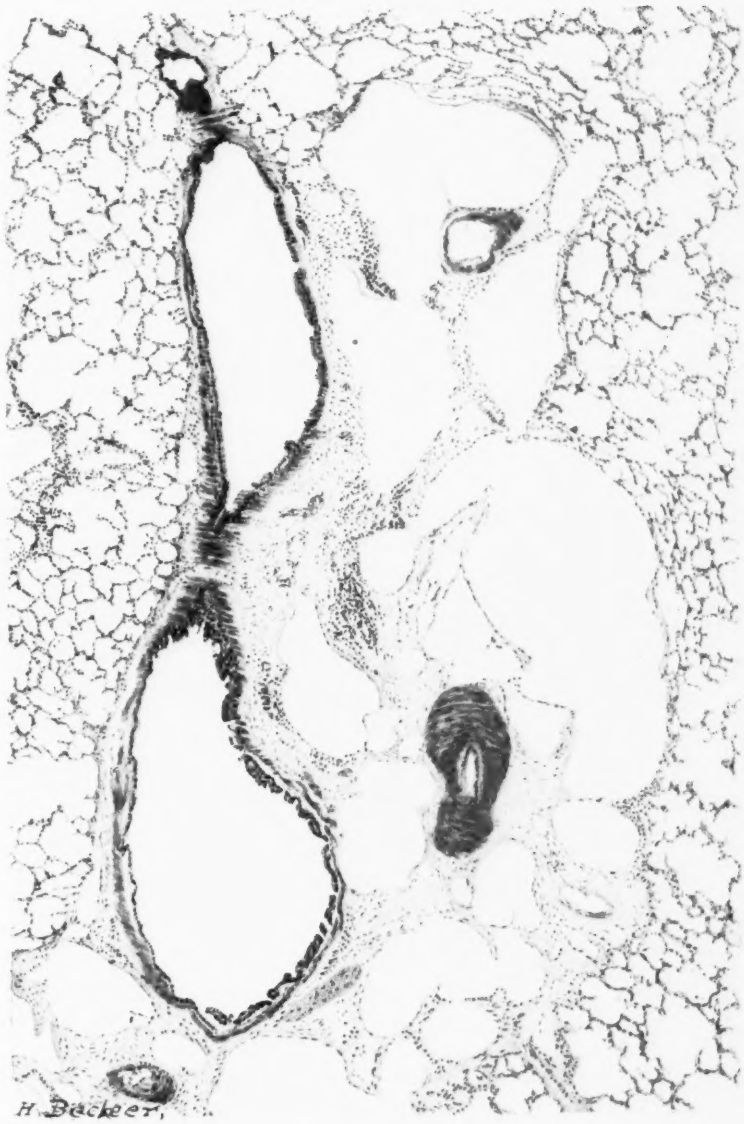


FIG. 7

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therefore, that the evidence here presented is of a kind to strengthen the idea of an "open" lung, with unusually free and active lymphatic flow. From figure 7, also, we may gain a more concrete idea of factors that contribute to this "openness;" here lymphatics are seen to be numerous and enormous. The entire picture in figure 7 is one that suggests a unique arrangement for the free passage of lymph within the guinea pig's lung. The slight amount of lymphoid tissue, loosely scattered in small collections, which is the norm for the guinea pig, is also well brought out in this drawing.

Our fundamental thesis would therefore seem to be well established; particles coming to guinea pigs' lungs, and deposited there, find (normally) lymphatic paths relatively unobstructed (by lymphoid tissue), and lymphatic flow (naturally hilumward) active, free and efficient; the entire mechanism promotes a relatively easy transference toward the root, and on to the tracheobronchials; if, then, the particles happen to be living tubercle bacilli, these should, until interfering circumstances arise, be hurried in large part toward the tracheobronchials; for this reason, early in the infection the tracheobronchials are likely to present an appearance of greater involvement than the lungs themselves.

As has been mentioned above, the critical test of such a working hypothesis should be the behavior of the guinea pig's lung toward tuberculous infection when its normal lymphatic structure is altered or upset. The determination of this eventuality required still further observations and experimentation. In outline, the next step involved attempts to create "blockings" of intrapulmonary lymph flow, or to increase or enlarge the points of arrest of particles along the lymphatic channels, and thus cause a trapping or "fixation" of more tubercle bacilli within the lung, with the consequent production of more tuberculosis there than in the normal animal's lung.

If one of our assumptions was sound, namely, that the characteristic "openness" of the guinea pig's lung was, in part, a resultant of a paucity of intrapulmonary lymphoid tissue, then it must follow that a sufficient increase of this tissue should erect barriers along the lymphatic paths, and thus bring about a condition of "closeness" of the lung. A natural consequence was to look for that agent which would cause an increase of lymphoid tissue.

As cited above, Miller had ventured the opinion that intrapulmonary

lymphoid tissue increased in amount under the spur or irritation of inhaled particles,—soot, dust, etc. His statement had reference, largely, to the situation in human beings. That for guinea pigs remained to be discovered; especially since it was deemed hazardous to apply, without further inquiry, rather incomplete observations of human anatomical relations to an explanation of conditions in the guinea pig, normally so scantily endowed with lymphoid tissue.

Laboratories engaged in the study of tuberculosis must keep their guinea pigs for unusually long periods, frequently for years. They are therefore privileged to see pulmonary anthracosis develop spontaneously in guinea pigs living a cage-existence. Accordingly, Willis investigated the deposition of foreign material in spontaneous anthracosis of guinea pigs, with results that appeared in our *Study VIII*. Older animals (he found) come to have larger amounts of intrapulmonary lymphoid tissue than younger animals; besides being laid down along the lymphatics (arterial, venous and bronchial) the pigment is concentrated in the aggregates of lymphoid tissue; these proliferate and enlarge enormously; and, at the same time, the lymphoid masses appear to be much more numerous than normally. What had undoubtedly happened was that lymphoid collections, consisting normally of only a few cells and therefore not noticeable on ordinary histological examination, had proliferated in response to the irritation, and become prominent components of the lung. At any rate, lungs, which without anthracosis exhibit hardly any noticeable lymphoid tissue, now displayed numerous collections of it. (See figure 8.) Besides, it was to be presupposed that the pulmonary lymphatics, "encased" throughout with an outside layer of dust, would have their calibre measurably reduced or their distensibility somewhat impaired.

Proceeding now intentionally to alter the lymphatic structures of the lung, Willis subjected guinea pigs to the inhalation of sifted *coal dust* for as long as one year. This work is incorporated in our *Study IX*. The dust was deposited, in large part, along the lymphatics and in the lymphoid masses, which proliferated. (See figure 9.) Meanwhile, Gardner, who has done so much to clarify our understanding of pneumonokoniosis and its relation to respiratory infections, mentioned, from time to time in his several papers, the proliferation which the guinea pig's intrapulmonary lymphoid tissue would undergo in response to various inhaled dusts. He did not study the particular problem that immediately concerned us, that is, the production of a lymphatic blocking

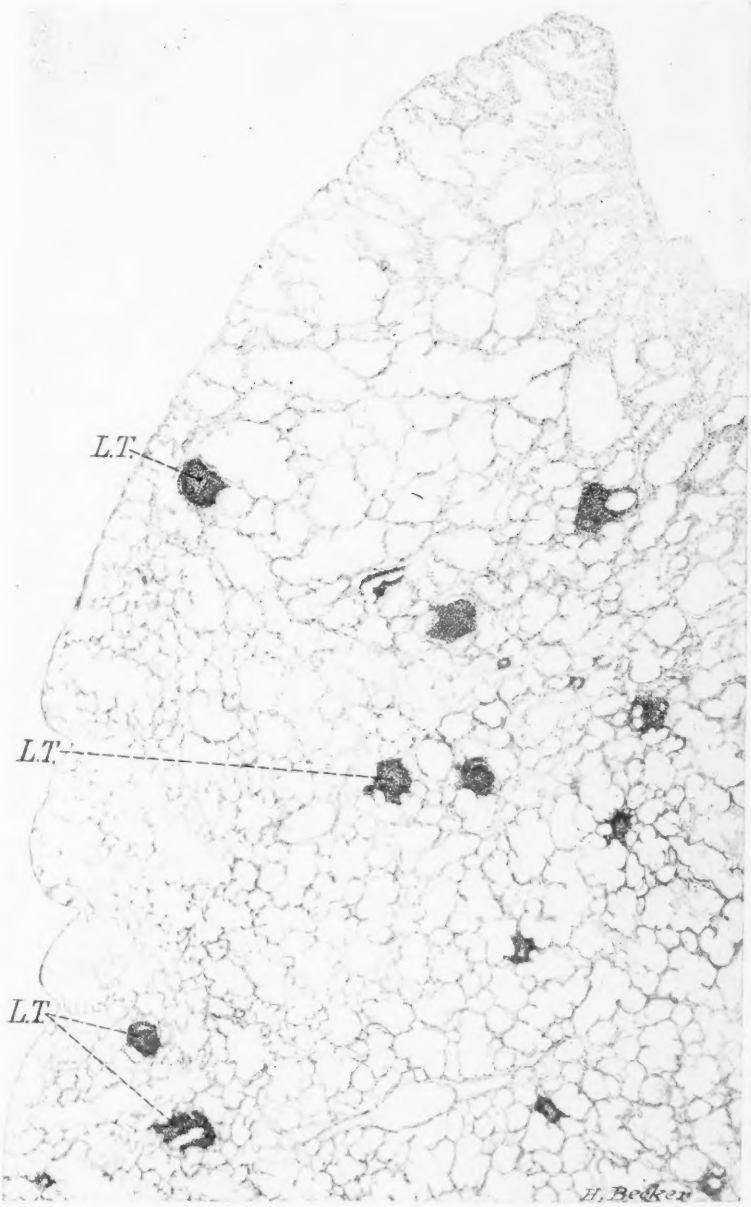

FIG. 8. REPRODUCED FROM OUR STUDY VIII, BY WILLIS, TO SHOW THE HYPERPLASIA OF INTRAPULMONARY LYMPHOID TISSUE THAT OCCURS IN SPONTANEOUS ANTHRACOSIS IN THE GUINEA PIG

Normally, and without dust in the lung, the lymphoid collections at the places shown would consist of only a few cells and be hardly noticeable on cursory examination. They now constitute the most striking feature of the section. (See text. *Cf.* with figure 7 of this *Study*.)

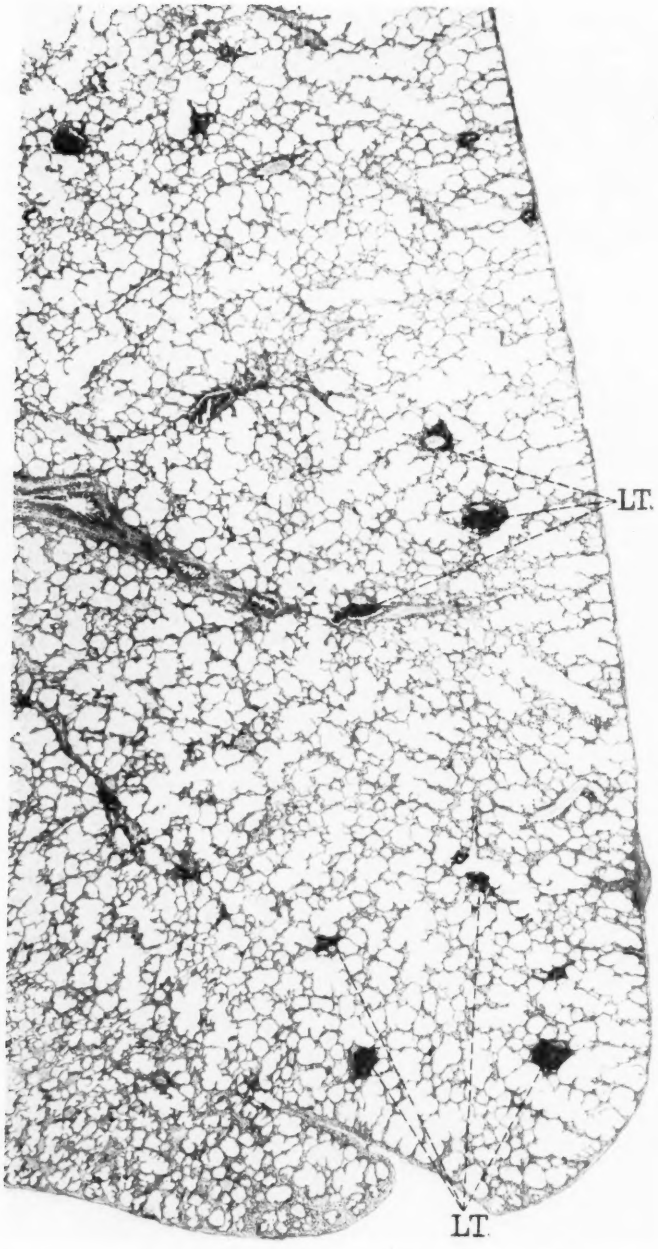

FIG. 9. REPRODUCED FROM OUR STUDY IX, BY WILLIS, TO SHOW THE HYPERPLASIA OF LYMPHOID TISSUE THAT OCCURS IN ARTIFICALLY INDUCED ANTHRACOSIS IN THE GUINEA PIG

(*Cf.* figure 7. See text.)

through the accumulation of dusts. He used dusts which bade fair to introduce complicating factors: calcium dust (marble) which is soluble in the pulmonary tissues, and siliceous dusts (granite and carborundum) which are directly traumatizing. Yet one gathers from his work that all of these dusts would cause lymphoid proliferation in variable degrees, especially granite dust. Siliceous dusts, when inhaled, quite likely bring about, as an end-result of their traumatic action, fibrosis of the lymphatics (a view advanced by several observers,—Haythorn, Watkins-Pitchford, Beattie, etc.), and thus contribute to any obstruction of lymphatic paths occasioned by an increase of lymphoid tissue.

Gardner found that the "dusted" lungs (with granite dust) of guinea pigs subjected to atmospheres of tubercle bacilli acquired more tuberculosis than did the nondusted lungs of animals placed in the same tuberculous environment. He was also inclined to believe that a theory of mechanical blocking of lymphatics, to explain a greater incidence of tuberculosis in dusted lungs, is correct for those cases in which prolonged exposure to dust had antedated infection.

Willis (*Study IX*) infected his guinea pigs *subcutaneously*, a method which should give less objectionable results (for our purposes) than infection by inhalation, and *after* preparation of the animals with prolonged inhalation of *coal dust* (carbon). Tuberculosis developed "somewhat more abundantly in lungs of animals exposed to dust than in those of normal animals,"—in a ratio of "about as three is to two."

It would appear, therefore, that notwithstanding quite significant technical difficulties and obscurities engendered by interfering factors (such as other complicating effects of physical and chemical properties of the various dusts, the arresting of bacilli by allergy in animals kept for more than a short time, etc.), it can be shown experimentally that any significant disturbance of normal lymphatic structure in the guinea pig, if it leads to blocking of "drainage" paths, will lead to an increase of intrapulmonary tuberculosis. In assembling our evidence in support of the hypothesis of the "open" lung in the guinea pig, and the influence of intrapulmonary lymphoid tissue in tuberculous infection, there yet remains the inquiry into whether the collections of this tissue are favored sites for the focalization and development of tubercle.

In this connection a citation from Miller, given early in this analysis, is enormously significant. "In every instance," he writes, "I have been able to trace their origin [that is, of miliary tubercles in a human lung]

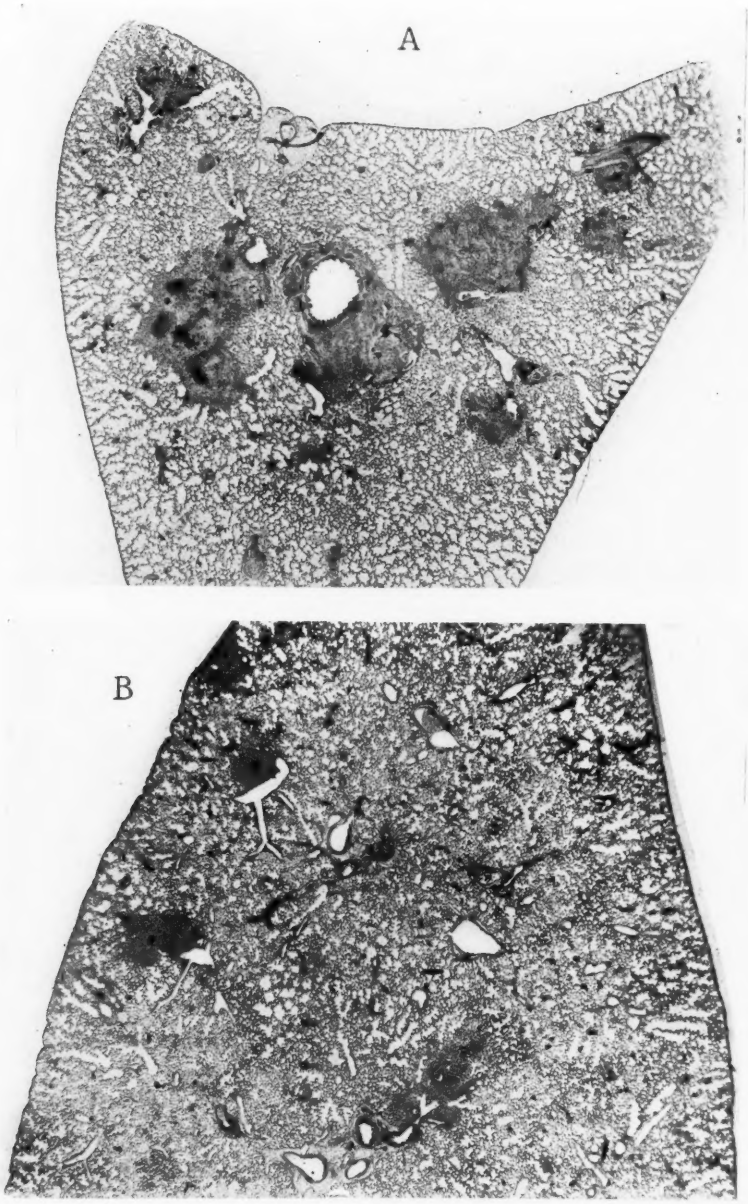

FIG. 10. REPRODUCED FROM OUR STUDY IX, BY WILLIS, TO SHOW THAT TUBERCULOSIS OCCURS AT THE SITES OF LYMPHOID TISSUE IN THE GUINEA PIG'S LUNG, AND THAT FOCI ARE LIKELY TO BE MORE EXTENSIVE IN THE DUST-CONTAINING LUNGS

A: From animal exposed to dust and inoculated subcutaneously with tubercle bacilli. *B:* From animal inoculated subcutaneously with tubercle bacilli, but not exposed to dust before inoculation. (See text.)

to one of the situations in which I have described lymphoid tissue as being present in the normal lung." One cannot help surmising whether the assiduous examination of similar types of tuberculosis by serial sectioning would disclose the focalization noticed by Miller to be the rule. If it so turned out, it would revolutionize our ideas of the pathogenesis of pulmonary tuberculosis.

Willis, in our *Study IX*, mentioned the tendency of both dust particles and tubercle bacilli to localize in the same situations, that is, in the lymphoid masses. Moreover, more tuberculosis developed in these situations in the "dusted" than in the undusted lungs. In Willis's experiments, in which inoculation of bacilli was subcutaneous, the germs entered the lungs by the pulmonary artery; yet, since they tended to focalize in lymphoid tissue of the bronchi, the topical relation of their foci to the bronchi was striking. (See figure 10.)

In the course of his studies on the healing of tubercle in rabbits which had inhaled tubercle bacilli, Gardner observed, as one of the most striking features of his histological sections, tuberculous involvement of "those midzonal lymphoid collections at points of bifurcation of bronchi and vessels," a comparatively late occurrence in the course of infection of his animals. The situation and time of development would suggest an origin from bacilli coming lymphatically from more peripheral points. But particularly prominent came to be the proliferation of lymphoid aggregations, from minute collections of cells which normally were hardly noticeable to large masses which almost usurped attention. These animals had not been exposed to dust. After healing occurred these masses persisted unchanged. They were by no means confined to the middle zones of the cross-section, as reference to Gardner's figures 26 and 27 will show. Here they are seen to be scattered thickly out to points just beneath the pleura. "Such nodules, arising from a pulmonary tuberculosis which has been allowed to heal, fail to infect guinea pigs when injected subcutaneously." Nevertheless, in the circumstances we must believe them to have arisen in response to tubercle bacilli, moving lymphatically from more peripheral points within pyramidal "drainage" fields and arriving (to quote Gardner) at "small collections of lymphoblastic cells located at the distal ends of the ductuli alveolares and at junction points of small peripheral veins."

Therefore, even in the guinea pig, with normally but little lymphoid tissue, there is a pronounced tendency for this tissue to fix and focalize tubercle bacilli, with results that become more apparent, as Gardner

says, "late in the course of the disease," when, it will be remembered, *pulmonary* tuberculosis begins to be prominent in guinea pigs. And the lymphoid tissue reacts to such effect that these "masses [again to quote Gardner] attain a considerable size, and become visible to the naked eye as collections of grayish pinpoint nodules."

Surely, we are justified as viewing the early manifestations of tuberculosis in the guinea pig, a condition of slight pulmonary with marked tracheobronchial-node tuberculosis, as conditioned by the peculiar anatomical relations of the animal's pulmonary lymphatic system: abundant and ample lymphatic channels, unobstructed by much intercalated lymphoid tissue and acted upon by an extraordinary intrapulmonary musculature, serve to "cleanse," as it were, with facility the lung of particles which enter it.

In the rabbit the part played by the intrapulmonary lymphoid tissue in the focalization of tubercle within the lung, and the factors governing the intralymphoid arrest of tubercle bacilli, are so plain that they can be determined by direct observation, and need but little collateral evidence to confirm them.

They are presented in our *Studies IV*, *XIII* and *XIV*. In *Study IV* Miller reports the rather astonishing discovery that the rabbit's intrapulmonary lymphoid tissue is vascularized by the pulmonary artery. It is obvious how important a bearing such an arrangement will have on all bacteria blood-borne to the lung. It assures a direct infection of the lymphoid tissue, in addition to whatever infection (bacteria) is being conveyed to the tissue lymphatically from other more peripheral points or foci in the lung. All pulmonary infection (bacilli) enters the lungs through either the air-passages or the pulmonary artery (except, theoretically, a negligible *quantum* by the bronchial artery). Bronchogenic infection (bacilli) in large part is at once mobilized lymphatically after it penetrates the epithelium; this part will be soon in contact with intrapulmonary lymphoid tissue. Haematogenic infection will also, for the reason stated above, go straight to the lymphoid tissue; and much haematogenic infection (bacilli) which is at first deposited elsewhere than in lymphoid tissue will again be mobilized lymphatically, and carried back to the lymphoid tissue.

Now the intrapulmonary lymphoid tissue of the rabbit is unusually abundant; and in *Study XIII* Willis shows that the tracheobronchial lymph nodes are insignificant. The animal's lymphatic paths *are*

punctuated by innumerable masses of lymphoid cells, masses again which are sizable in all locations. Therefore, we have in the rabbit's lung a lymphatic apparatus that is almost perfectly equipped to receive, to intercept and to retain particles. Therefore, we find its intrapulmonary tuberculosis prominent, and prone to extensive development, and tuberculosis of its extrinsic lymph nodes, the tracheobronchials, slight.

All the features mentioned may be observed in the illustrations of *Study XIV*. There are the extreme pulmonary tuberculosis, the profusion of intrapulmonary lymphoid tissue and the fixation of tubercle bacilli within the lymphoid tissue almost immediately (one and four hours) after intravenous inoculation. At a sufficient interval after inoculation, when we must believe that all bacilli of primary infection must have settled out and have "found" their place, we see *tubercle* focalized preponderantly in the lymphoid tissue. With time, also, those lymphoid foci that are more central become the more extensive ones; added to, no doubt, by bacilli transferred lymphatically to them from more peripheral points.

This positive demonstration of the rôle which the lymphoid tissue plays in the fixation of pulmonary tuberculosis in one animal species serves to strengthen all the more our ideas of the opposite case in the guinea pig. It is the best proof we can have that the lungs of the latter animal are spared infection because they possess but little lymphoid tissue to intercept the bacilli. For if it is true that a prime function of the tissue, when it exists in adequate amount, is to fix infection, then we must also believe that its absence or insufficiency permits infection (bacilli) to remain unattached and to pass on.

THE MECHANISM OF TUBERCULO-IMMUNITY

Study VI demonstrated the marked tendency for tubercle bacilli to migrate from their point of entry in the nonimmune animal, and the extreme rapidity and completeness of their further spread within the first few days after infection; findings that, as mentioned above, have been confirmed by Gardner, by Rensch and Moore, and by others. In *Study X* Willis worked out with greater precision the rate of the more immediate dissemination of tubercle bacilli in nonimmune guinea pigs. Within the first hour after infection the germs had, in some instances, been moved beyond the field of inoculation, and by the end of the third hour they had always passed further. At some time between ten and

twenty-four hours they had traversed the few inches between the site of inoculation and the first chain of lymph nodes, and had arrived at the latter destination.

But, as was shown by Willis in *Study XI*, the one to three hours required to clear the site of infection in the nonimmunes was, in *immune* animals, lengthened to from a minimum of four days to a maximum of seven days; while the normal one-day passage from site of inoculation to regional lymph nodes was protracted to from two to three weeks.

Similarly, as related in *Study XII*, Krause found that in immune guinea pigs, inoculated subcutaneously, a great delay of transmission to internal tissues and organs attended the movement of tubercle bacilli. The journey from groin to lungs, tracheobronchial nodes and spleen, taking four days or less in the nonimmunes (*Study VI*), became a matter of from three weeks to thirty days in the immunes.

The significant demonstrable *late* happening in tuberculo-immunity was therefore proved to be an enormous retardation of the movement of bacilli from the portal of entry to important and customary places of focalization in the body, a consequent much-delayed first appearance of tubercle, and a more leisurely progressiveness (a chronicity) of disease. The term of fatal issue was stayed from the usual three months or so, as experienced in nonimmunes, to ten and eleven months in immunes.

In *Study XII* may be found a more or less labored discussion of possibilities that may conceivably be concerned in tuberculo-immunity to bring about so pronounced a slowing up of bacillary dissemination in the immunes. It should be unnecessary again to traverse the same ground here; and the interested reader is referred to the *Study* for a detailed assembling and analysis of the evidence concerned. It is enough to repeat here that, after a fairly exhaustive review of the data available, we inclined to the opinion that the temporary check to bacillary metastasis observed in immune animals resulted from some barrier interposed by them against the further passage of bacilli, and that this was erected to greatest effect at or near the portal of entry. For the reasons there presented we could not be convinced that tuberculo-immunity set into play *specific* immuno-lysins, which killed and destroyed bacilli.

If our interpretation of effects is sound and our rough demonstration of the character of the immune force is reasonably correct, we may be at once asked to define what our "barrier" of immunity may be. The reader who is at all familar with the publications of the last ten years from the Kenneth Dows Laboratory will, no doubt, anticipate the answer.

For, throughout this time one of our major interests has been concerned with investigations actuated by the working hypothesis that tuberculo-immunity is a function of tissue allergy, the essence of which in operation (allergic reaction) is an accelerated and exaggerated tissue response to reinfection; a response, which serves to hem in the bacilli of reinfection and thus interfere with the immeasurably more rapid migration characteristic of them in nonimmune animals.

The development of this thesis, step by step, and its gradual elaboration and refinement, to accommodate newly discovered evidence, are to be found in publications included in the list of *Other Literature Cited* appended to this paper. With the lapse of time, and its greater accumulation of observations, we have come more and more to believe that the idea, in principle, is sound, rests upon a secure foundation of fact, and will continue to be as fruitful in explanation and prediction as it has been in the past. Indeed, our *Studies VI, X, XI* and *XII* were undertaken largely to test the validity of the hypothesis. For, if it was well-founded, the allergic "barrier," which we had postulated for the immune animal, should be capable of being shown to check the spread of tubercle bacilli. First, therefore, it was necessary to learn, with fulness and precision, the routes and rates of transportation in the normal nonimmunes, which, once determined, gave us a basis of comparison for similar features in the immunes.

In summary (see particularly *Krause and Peters*), we may repeat here that both tissue allergy and immunity are attributes of animals with tubercle; that the allergic reaction is set into play by the tissue contact of immune animals with dissociated tuberculo-protein or with tubercle bacilli, living or dead; that its characteristics are prompt appearance and vigorous course of a tissue response, marked by acute inflammation, that is followed by an accelerated development of characteristic nodular tubercle; that the effect of these extraordinarily rapid and exaggerated reactions is to fix bacilli and thus impede their mobilization from the site of infection; and that the visible ultimate consequence is that appearance of delayed, abortive or more chronic disease which answers to our representations or concepts of immunity.

Of course, underlying all allergic phenomena that become visible to us are biophysical and biochemical processes, and interactions of micro-organism and host, that are, as yet, thoroughly obscure; and back of these are the still more basic mysteries of such problems as constitution and irritability of tissues and the fundamental nature of the stimuli

exerted by the germ, and so on; but these are ultimate problems, which lie far beyond our present ken, and which, solved, would promise to take us close to a concrete understanding of what life is itself. Before we venture on next steps, it will make these immeasurably firmer and more certain of arrival, if we can set out from facts that are demonstrably beyond dispute.

We believe that the new facts presented in these *Studies* (*X*, *XI* and *XII*), when correlated again with what has appeared in our former publications, places on a still more secure foundation the general idea that through the allergic reaction tubercle bacilli are "fixed," as it were, at points of deposition in the tissues and are consequently hindered in metastasizing; and, as we have stated, one effect of this process will be an end-result which typifies immunity. Yet, we would at once make clear that, until further evidence is forthcoming, we would not restrict our ideas of the elements contributing to immunity to this single demonstrated result of allergy. The latter's effects, immediate and remote, are not so simple that they may be comprehended within the concept of a single force acting mechanically.

For instance, by far the most prominent feature of the allergic reaction that is immediately visible is the acute inflammation by which it is recognized, and only by which it can be recognized. Now, any acute inflammation must, of necessity, always disturb local tissue relations in varying degree; local fluid content, local cellular content, local concentration of solids, local pressures, local blood supplies, are always altered. Under the circumstances we cannot think of the locally contained tubercle bacilli in any other way than of their being variably influenced by this thoroughly abnormal tissue environment. Nor need we bring in ideas of specificity of interaction in attempting to imagine what *might* happen to tubercle bacilli in an inflamed *milieu after the allergic reaction has got under way*. We may *suppose* that unfavorable osmotic relations may lead to the death and disintegration of bacilli, emphasizing meanwhile that such an event need not involve specific immuno-lysis; we might even predict the occurrence of such modifications of nutritional and "respiratory" requirements as would lead to the same result; we can think of the possibility of innermost bacilli situated in necrotizing tissue dying while more peripheral germs in touch with healthier tissue survive, or, what is more likely, *vice versa*. At all events, until the contrary is proved, we have every reason to believe that acute inflammation, nonspecifically and of itself, can exert profound biochemical and biophysical effects on

tubercle bacilli. But we shall *know* little about all this until we have approached the subject with satisfactory experimentation.

But, to return to the matter of the "fixation" of tubercle bacilli as a consequence of the allergic reaction, and the bearing this may have in tuberculous infection.

It must be plain that, endowed with such a capacity to fix bacilli, organs, which by nature are relatively "permeable" from a lymphatic point of view, may be converted, as the animals become immune and allergic, into organs in which tubercle bacilli in movement may be promptly arrested and retained. To all intents and purposes, therefore, the immune guinea pig's lungs will be not unlike normal rabbits' lungs in their behavior toward incoming tubercle bacilli; while, as rabbits also become immune, the native capacity of their lungs to arrest and hold bacilli will be magnified.

Our experience has yielded us observations to *indicate* that such a physiological change actually does take place in the lung of the guinea pig that has become immune. A number of years ago we performed intravenous inoculations (tubercle bacilli) of immunized guinea pigs, as well as of nonimmune controls, and were then greatly impressed by the regular appearance of much more tuberculosis in the immunes' than in the nonimmunes' lungs during the first two weeks after infection. But, difficulties of exact comparison lay in the fact that visible changes (foci) in allergic animals arise much earlier than in the nonimmunes and are, at first, more prominent and extensive. A satisfactory experiment of this kind would require the nicest adjustment of "dosage" for the proper interpretation of results. Since our animals were being studied in an altogether different connection, and our observations were more or less by the way and not rigorously controlled, the ideas which we then derived on the subject under discussion were no more than unconfirmed inferences.

In the prosecution of our *Study XII* we again had hints that may be pertinent here. From our *Study VI* we had learned that for a short time after the subcutaneous inoculation of nonimmunes their excised tracheobronchials were likely to set up earlier tuberculosis than the lungs, when these tissues were inoculated into fresh guinea pigs. The experimenter will find not a few exceptions to this outcome, but, if the proper time relations are observed, we believe that the general rule will hold. When, however, we came to appraise the bacillary content of the tissues of immune guinea pigs by inoculating these into new animals, we

were much impressed by the circumstance that invariably the infection produced by the lungs appeared before and kept ahead of that caused by the tracheobronchials of the same animal. Such a result would suggest a greater content of bacilli in the lungs than in the tracheobronchials of immune guinea pigs. But, to determine this point more definitely would require exhaustive and rigorously controlled experimentation directed toward clearing up the particular point; and would involve, no doubt, the employment of a wide range of infecting "dosages" of bacilli. Again, we can have obtained only an impression or inference from this experiment.

At all events, we would predict at present that a natural facility of passage of bacilli through an animal or organ, due to any cause whatever, would be interfered with by allergy, acquired when the animal became tuberculous. As a classical example of the result of this opposition of factors of infection we might evoke two contrasting familiar results of intestinal infection in man. The infant drinks tuberculous milk, and falls ill with *tabes mesenterica* with little or no noticeable enteritis. The pulmonary consumptive, in late childhood and afterward, has his lung disease complicated by *enteritis*, with prominent mesenteric tuberculosis much the more unusual event.

In prosecuting this series of *Studies* it was our purpose to gain as precise information as possible on two, and only two factors concerned in tuberculous infection. In the above discussion we have analyzed these, and have tried to give them their proper place and weight in the general "scheme" of infection. As we conclude this part of our work we may take the opportunity to set down, in outline and in summary, our ideas of how infection, broadly and comprehensively, should be viewed.

From a practical point of view the issue of tuberculous infection is the most important, perhaps the all important, thing for us. Contributing to the issue are undoubtedly almost innumerable factors. There are attributes of parasite: type, generic and individual virulence, quantity, repetition of reception, etc. There are the forces of environment, and these are boundless, in their play upon the host, both at the time of infection and at any and all times during the tenure of the infection.

There are, in addition, the factors that concern the recipient of the infection. The portal of entry and the place where the bacilli first come to lodge in tissues are important, as well as the avenues traversed from one point to the other. Then enters the factor of native susceptibility

of soil and of general bodily constitution, both inherited. Now, as we have seen, organic structure may be decisive in localization and the further evolution of infection. No doubt, among determinants may be classed the anatomical character of the capillary bed in any particular place: its size and complexity, its tortuosity and its physiological activity. We may also speculate concerning biophysical and biochemical factors, such as the influence of the various secretions of the body or of the density and solidity of the several tissues and organs.

We begin to find ourselves asking why, for instance, are tuberculosis and syphilis so opposite in the focalization of their manifest lesions. Lymphatic tissue, it would seem, falls prey alike to each. We have learned to look upon syphilis as a generalized infection, obtruding itself only here and there in scattered discrete foci or in particular organic systems. With increasing knowledge we incline to a not dissimilar view of tuberculosis. But, apart from the lymph nodes, the differences of *significant* focalization of tuberculosis as against syphilis are striking. Syphilis would seem to "prefer" glandular tissue, for instance, the liver; tuberculosis, to shun it. The commonest seat of tuberculosis, the lungs, is quite likely among the rarest sites for *discrete* syphilis. Syphilis is eminently a disease of vascular tissue; tuberculous arteritis is almost unknown. Tuberculosis of the serous membranes is a familiar disease; not so syphilis. It is tuberculosis of the joints and shaft, but periostitis in syphilis; tuberculous meningitis, but syphilitis encephalitis and myelitis; tuberculous epididymitis, but syphilitic orchitis.

We may be sure that the explanation of these obscure contrasting localizations, when it shall have been found, will go a long way toward defining for us really decisive factors in tuberculous infection also.

Numerous and diverse, as we have just stated, must be the factors which contribute to the more immediate results of primary infection. And, when infection is once established, there enters the modifying influence of allergy, acting always no doubt significantly, and at times decisively.

NOTES AND SUGGESTIONS CONCERNING HUMAN TUBERCULOUS INFECTION

On the basis of our *Studies* and scattered observations culled from the work of others, we may be permitted to piece out schematic representations of what probably takes place at the time of human pulmonary infection and after tubercle bacilli have settled in the lung.

It is beyond dispute that the lungs are infected, both primarily and metastatically, via the air-passages and the blood-vessels. It certainly cannot be considered as settled whether they are infected via the lymphatics; as, for instance, by a direct lymphatic path from nasopharyngeal and cervical adenoid tissue (tonsils, neck nodes), or by retrograde lymphatic passage from the hilum and tracheobronchial nodes. The anatomist, trained in working out vascular arrangements by the use of injection masses, and familiar with technical difficulties and the fallacies that inhere in work conducted by any but the most expert hands, will be slow to accept ideas that involve the operation of particles carried backward against the normal direction of lymph-flow. (See particularly Most on *Lymphatics of the Upper Thoracic Aperture*, etc.)

The physiologist and the clinician are likely to be more easily convinced: they will think in terms of a ceaselessly moving organ that is ever subject to violent changes of internal pressure (through coughing, physical exertion, etc.), which may reasonably be imagined to reverse normal lymphatic relations. In this connection it must also be remembered that we really do not know the exact conditions of lymphatic flow for every part of the lung at the several ages of man. Indeed, we have assumed a great deal on a very slender basis of *direct* knowledge. Nor shall we be much more enlightened until some man, or body of men, applies the years necessary to serial sectioning of much of the human lung, right and left, and lobe by lobe, to make sure for us whether the lymphatic flow of all lobes is alike, and whether human relations correspond to those in the animals usually studied. Of course the task is herculean; but there is probably no more royal road to the solution of the problem. On clinical-pathological-roentgenological evidence, derived from the cursory methods ordinarily employed, one is almost obliged to believe that, in at least the upper lobe of the human lung, lymph flows from root to interior; but, mindful of what anatomical facts we have, one shrinks from making the deduction.

It would seem that those inhaled particles (bacteria) which remain in the lung settle out, by "preference," in the terminal subdivisions of the respiratory tract that are subpleural or nearby. In his studies on healing, which involved a technique of inhalation, Gardner repeatedly refers to a primary and earliest development of tubercles out at the periphery of the lung, and beneath the pleura; and goes so far as to say that we must assume that "there [that is, "the pleural regions"] the primary *infection*[2] develops."

[2] Italics A. K. K.'s.

Anyone, who has observed the early intrapulmonary disposition of dust in animals allowed to inhale it, will be prepared for such a focalization as Gardner describes. If guinea pigs are killed a short time after a single transitory exposure to coal dust, the dust is prominent in the terminal alveoli. Not much, if any, is to be found in relation to other structures of the lung. With time and repeated "dusting," more and more particles accumulate within the depths of the lung. After exposures of three hours a day and thirty days following the last inhalation, dust becomes noticeable in the pulmonary lymphoid tissue: "*this is the earliest sign of dust in lymphoid tissue*" (Willis, *Study IX*). Making all due allowances for such differences of ease of movement, localization, and lymphatic passage as may attend the enormous dissimilarity of size of dust particles and tubercle bacilli, we must believe that the fate of inhaled bacilli would be roughly comparable.

Why are the deposited particles mostly confined, *at first*, in the terminal alveoli (roughly from the alveolar ductules to the air sacs)? For answer, we may call upon the ciliated epithelium, which, functioning normally, is no doubt capable (unless the "load" is too great or heavy) of keeping the air-passages clean, and preventing deposition in those parts proximal to where the epithelium changes (respiratory bronchioles).

Now, at these terminal points, where dust will first settle out *in a normal lung*, there are no lymphatic vessels, nor is there lymphoid tissue. (See our *Study II*, by Miller, especially figure 1, and *Study III* by the same author.) Bronchial lymphatics originate in the walls of the alveolar ductules; between this subdivision and the termini of the air-passages, the air-sacs or so called *alveoli*, the air-passages are "lymphless." Again, it is at the distal end of the alveolar ductules that the last *bronchial* lymphoid tissue is to be seen; beyond this point it is absent.

If tubercle bacilli have gained an alveolus, or any point between this and the alveolar ductule, some may presumably settle permanently in a septum back of the epithelium; if they do and if they remain alive, there results a cellular reaction *in situ* (tubercle) of greater or less moment. This should be much more likely to occur in the allergic animal (in bronchogenic metastasis, for instance).

But, undoubtedly, many tubercle bacilli, perhaps most of them, having arrived at places designated above, are picked up and mobilized by cells. Miller is thinking of some such disposition when, from direct observation, he writes, "It is not uncommon to find phagocytes laden with particles of carbon, which they have picked up within the alveolus,

lying close to, or just penetrating, the wall of an alveolus, on their way to deposit their load in the lymphoid tissue." He is describing what happens in the human lung. It is true that he is referring to that small peripheral portion of the lung that comes within the pleural zone of lymphatics, but there would seem to be no reason why the description cannot apply to all parts of the lung.

If cells carry the germs beyond the septal wall of an alveolus, they put the bacilli outside the primary anatomical unit in which the bacilli were first arrested, and in relation with another unit that is juxtaposed. The point in question may be at a part of the second or apposed anatomical unit that is lymphatically supplied, that is, at a part proximal to the atria. If so, these bacilli may be taken into lymphatics, and be put on their way hilumward, with frequent opportunities of focalization in collections of lymphoid tissue in between. Bacilli, that come to rest (temporarily) in the alveolar ductule or respiratory ductule of the first anatomical unit, can be carried directly into the lymphatics of this unit.

It becomes clear, therefore, why very first changes (after bronchogenic infection) may be noted subpleurally and in association with the alveoli. Bacilli, which are deposited here, do have a chance of gaining lymphatic channels and thus being moved variable distances from their original stopping-places; but the chance is not nearly so great as is that of bacilli originally deposited proximal to atria. Those that stay in the alveoli may initiate foci there, and early after infection the disposition here is prominent.

But any measurable development of such alveolar foci of tubercle is likely to put them in corporate communication with another apposed primary unit, when the bacilli of the focus will be subject to the same eventualities mentioned in the case of those which may have been carried by cells through the alveolar septum. Indeed, unless the alveolar focus is very primitive and minimal, it is difficult to conceive of tubercles being confined to the single anatomical unit of their origin. In this connection we may recall that the tubercle, from which Miller made his beautiful reconstructions of our *Study II*, measured approximately only 2 × 3 mm.; yet one of Miller's main conclusions was that "the tubercle does not belong to any single system of air spaces." If we will only keep visualizing pulmonary histological structure in its three dimensions, and remember that everywhere it is an arrangement of minute bending and sacculated "tubuloids," crossing and recrossing one another, as primary anatomical units, to a degree and at every angle, and remember

also that distances and relations between the several elementary components are always microscopic, we shall see how all bacilli and foci must be within ready access of lymphatics.

Bacilli, which come by the blood and are deposited in the lungs, will first embolize in the smaller vessels, no doubt, and then be carried out of the lumina. The point may be within an alveolar septal wall, or it may be in relation with any other subdivision of an air-passage. The subsequent career and destination of the bacilli must be conceived of as similar to those of air-borne bacilli.

Every lung has, of course, its own inherent dynamics, which will govern its lymphatic flow and the transmission of particles (bacilli) along its lymphatic paths. But, given bacilli or tubercle out in the lung and given access of these to lymphatics, the freedom, ease and rapidity of bacillary movement by lymphatics toward the root will be conditioned, as we have seen, by the "openness" of these lymphatics and the integrity of the entire pulmonary lymphatic system.

The human infant is born with a lymphatic system, which, in general, is open and permits the readiest transmission of foreign particles. With increasing age comes a growth of adenoid tissue (as, for instance, the tonsils), and a denser structure of lymph nodes and lymphoid tissue normally present throughout the body. After maturity and in the later ages of life, lymphatic tissue undergoes regressive changes, and atrophies (as, again for instance, the tonsils, follicles of the vermiform appendix, etc.). (See *Krause, Human Resistance to Tuberculosis at Various Ages of Life.*)

Few parts of the lymphatic system can be so much exposed to the reception of foreign particles as are the pulmonary lymphatics. In our civilization the ordinary city-dweller is continually breathing in an atmosphere surcharged with them. Much of this intake of dust and soot, if it passes the pulmonary epithelium, is deposited along the pulmonary lymph vessels; the rest is collected in the tracheobronchial lymph nodes and the intrapulmonary lymphoid tissue. We arrive, in effect, at every imaginable gradation of foreign-particle-containing lung, from the barely perceptible streaking and spotting of the surface, that appears in the person who has lived a long life mainly in the country, to the markedly engorged, discolored, and even distorted lung of the life-long miner and quarryman, whose lung will grate the knife in the cutting of it.

The lymph vessels, which receive all these particles, will be variably affected, but one result will always be to impair their integrity and their permeability. From birth to maturity, the lymphoid tissue increases in amount quite naturally, no doubt, and without reference to any intake of foreign particles, just as happens with all lymphoid tissue. But under the spur of inhaled particles it increases much more than would otherwise be the case. Very likely, also, it proliferates in response to the irritation of the numerous respiratory infections, that are our common lot, just as Gardner found it reacting enormously and rather permanently to inhaled tubercle bacilli of low virulence, and just as we find the tracheobronchial lymph nodes influenced by the whooping cough and measles and other infections of childhood.

Accordingly, the normal evolution of the lymphatic system and the ordinary experience of all of us combine to change gradually the structure of our intrapulmonary lymphatic apparatus. There is unpublished work in the Anatomical Laboratory of Yale University to show that the lungs of the human foetus at seven months have very little lymphoid tissue. Miller states that it "increases from childhood to old age." Without considering such factors as normal development and respiratory disease he attributes the increase as "largely due to the irritation arising from the constant inhalation of irritating substances." He pictures lungs of children four days and seven years old, and of an adult of thirty-eight years, and, in addition, generalizes from observations made on the lungs of a number of adults as old as sixty years and more. Citing Shingu, to the effect that pigmentation of the lung is not to be observed before the twenty-third day of life, he finds a material increase of lymphoid tissue at seven years, marked proliferation in specimens at thirty-eight years, and the most marked development in old age.

After a consideration of all of the above facts, it is not difficult to understand why the manifestations of *discrete* pulmonary tuberculosis in early childhood are *typically* more prominent at or near the root of the lung. It must be because air-borne or blood-borne bacilli, that come to the lung, find passage through it relatively unobstructed. With increasing age come impediments along the lymphatic path; with increasing age, also, and with foci at the root, at the apex of the "drainage" basin, come further abnormalities of lymphatic flow, of a kind to promote slowing and stasis of the stream; with increasing age and its larger probability of tuberculous infection, comes allergy with its tendency to "fix" bacilli out in the lung where they settle. With increasing age, therefore,

comes a combination of factors, as has been demonstrated, to favor the appearance of manifest and more prominent discrete tubercle out in the lung. And it is this that we call the adult type.

There is not infrequently recorded a similarity between the situation of a certain type of pulmonary tuberculosis (frequently fulminant) in primitive peoples, newly introduced to our civilization, and that typically met with in our children; that is, a tuberculosis largely confined to the hilum, or originating *clinically* there. Writers, in presenting such cases, often speak of the disease, by reason of its location, as typifying little or no resistance on the part of the patient. It is difficult to follow the reasoning back of such a characterization, if indeed there has been any reasoning practised; for usually the statement is made *ohne weiteres*. Of course, the semisavage, lacking antecedent contact with tuberculosis, may have been natively the least resistant of men; and, of course, as we view the possibilities, a root localization may have stood for a lack of allergy, and therefore for an inability to focalize bacilli in the lung, and thus for an absence of specific immunity. But it is doubtful whether the writer ever attempts to reason so precisely. From what one can gather, he apparently associates hilum tuberculosis with innate and native oversusceptibility to the infection.

We cannot see the slightest warrant for such an assumption, although we can think of a good deal of the best of evidence that would belie it. If a hilum focalization and origin of clinical tuberculosis are the marks of feeble resistance, then most children with pulmonary tubercle (and many with other forms) should be "bad risks;" for the vast majority of these children have most of their pulmonary changes at the root. But, if the facts are to guide us, we find that these children are, in truth, the best of all tuberculosis "risks." For instance, if we compare the tuberculous-infection incidence with the tuberculosis mortality among the males of New York City, we find that in children (ages 5 to 12) the former (years 1915–1920) is to the latter as 800 is to 1, while at ages 40 to 60 the ratio is about 450 to 1. One of the few invariable features of tuberculosis mortality is that all over the world it always has been lowest in children—at that time when pulmonary tuberculosis is most prominently hilar.

As concerns the members of more primitive civilizations than ours, we would predict that pulmonary infection in them would tend to "gravitate" to the hilum for the same reason that it is most likely to be found there in our children; that is, freedom from smoky and dusty

atmospheres and from our own much more common respiratory infections will tend to leave the lungs of the dweller in the open in their original clean and "open" state.

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THE PULMONARY EFFECTS OF INTRATRACHEAL INJECTIONS OF TUBERCLE BACILLI AND BLOOD IN RABBITS

AN EXPERIMENTAL STUDY OF THE FACTORS RESPONSIBLE FOR ROENTGENOGRAPHIC CHANGES FOLLOWING HAEMOPTYSIS IN PULMONARY TUBERCULOSIS[1]

CHARLES R. AUSTRIAN AND HENRY STUART WILLIS

Of the many types of roentgenographic changes seen in pulmonary tuberculosis, few are of greater interest or have occasioned more discussion than that variously designated as *diffuse mottling*, *miliary seeding*, *soft mottling*, etc.

The exact nature of the lesions responsible for the so called soft, or (more aptly designated) ill-defined, hazy, small shadows occasionally demonstrable throughout one or both of the pulmonary fields in roentgenographs of the lungs is in dispute. Regarded by some as tubercles, the presence of them has been considered portentous. When interpreted by others, who have accepted Amberson's view, as due to perifocal or allergic inflammation consequent upon the implantation of tubercle bacilli into sensitized tissue, their significance is deemed less grave.

It is well known that, occasionally after an haemoptysis in pulmonary tuberculosis, roentgenographs of the lungs show this scattered mottling, sometimes termed *miliary pulmonary tuberculosis*, and that in the course of time, *pari passu* with or even antedating progressive improvement, these shadows fade or may even disappear. Such was the sequence of events in patient *M. K.*, a youth of 21, who enlisted in the A.E.F. in 1917.

He had not been intimately exposed to tuberculosis in childhood, and had shown no tendency to infections of the respiratory tract nor symptoms of any latent infection. In camp he developed measles; and, six months later, after a hike in France, although apparently in normal condition, he had a frank haemoptysis. Fever, productive cough and malaise developed, and

[1] From the Kenneth Dows Fund for the Study of Tuberculosis, of the Johns Hopkins Hospital and University.

persisted until the time when one of us examined him in May, 1918. At that time there were signs of an actively infiltrating disease at the apex of the left lung; and râles, without associated changes, were heard throughout the entire left side of the chest. Tubercle bacilli were demonstrated in the sputum. X-ray examination showed numerous small hazy shadows throughout the left lung. During the course of the next three months the symptoms subsided, and within the next three years the signs cleared, and roentgenographically all evidence of infiltration disappeared except at the apex of the left lung.

The course of events in this patient awakened anew our interest in the anatomical nature of the lesions that cause the scattered shadows seen occasionally in roentgenographs of the lungs taken promptly after an haemoptysis. In some instances, such shadows are undoubtedly due to tubercles, as is indicated by their late appearance, their subsequent coalescence, the progressive course of the disease, and the evidence of consolidation or of cavitation that may follow. If, as in this patient, apparently complete restoration of normal conditions results, it may be inferred that healing of tubercle has occurred, analogous to that described in animals by Gardner and in patients by Amberson; or, more plausibly, that the shadows were due to an inflammatory exudative type of tuberculous lesion that may be completely removed by absorption, a mode of healing that is known to take place especially when allergy is well developed. In accord with this latter view, the hypothesis was suggested that the shadows were neither of aspirated blood alone, nor of anatomical tubercle alone, but of areas of acute inflammatory exudation, such as are known promptly to develop when reinfecting bacilli are implanted in a sensitized tissue. The purpose of the work reported was to test the validity of this theory.

The procedures adopted to simulate clinical conditions were the following:

Healthy rabbits were *subcutaneously* infected with a strain of tubercle bacilli of bovine type (B1), grown from two to three weeks on Petroff's medium, and suspended in physiological salt solution. From time to time after the inoculation, the chests of such animals were X-rayed. From the first, technical difficulties were encountered: even when respiration was inhibited by holding a flask of ether before the nose, the films of infected rabbits failed sometimes to show evidences of pulmonary infiltration, although anatomical study showed gross lesions in the lungs. Inasmuch as it seemed possible that the vibration of the pulmonary tissue caused by the rapid action of the

relatively large heart might be an interfering factor, cardiac standstill was brought about in addition to the induced apnoea. To bring about these two conditions synchronously, many procedures were tested; and, of them all, electrical stimulation of the vagus proved to be the best. An electrode was applied to the midcervical region over the carotid sheath; but even when this method was utilized the film usually indicated less disease than was demonstrable at necropsy. The most satisfactory films were obtained when the exposures were made for $\frac{3}{4}$ second, with a spark gap of 1 inch, at a distance of 24 inches, with a current of 5 milliamperes, using a double screen with film.

After pulmonary changes had developed as a result of the subcutaneous infection, in order to parallel the conditions that exist when an haemoptysis occurs clinically, blood was injected directly into the trachea of the animal. The blood used for injection was aspirated from the heart of a rabbit, and, in order to inhibit coagulation temporarily, it was drawn into a syringe containing a solution of *heparin*, in the proportion of one milligram of heparin to each 20 cc. of blood.

In the experiments, the following procedures were performed:

1: Rabbits with pulmonary tuberculosis were injected intratracheally:

a: With normal blood.

b: With blood to which a suspension of tubercle bacilli in physiological salt solution had been added. The bacillary suspensions were prepared as follows: The microörganisms in physiological salt solution were centrifugated, filtered through cotton, and diluted to contain from 7 to 12 bacilli to the oil-immersion field. One or one and one-half drops of this suspension from a 22-gauge needle were added to 1 cc. of blood.

c: With physiological salt solution to which were added tubercle bacilli in the same numbers as in the experiments in which blood was the menstruum.

2: Normal rabbits were treated in the same manner as the already tuberculous animals.

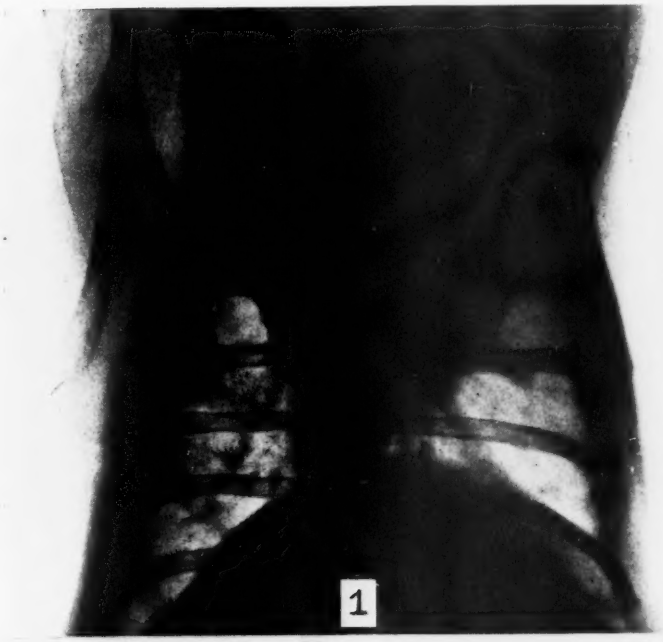
The lungs of animals that received intratracheal injections were examined with the X-ray (1) before injection, (2) immediately thereafter, (3) on each of the succeeding 5 or 6 days, and (4) after periods of one to three weeks.

About eighty experiments were made.

FIG. 1. ROENTGENOGRAPH OF A PREVIOUSLY INFECTED RABBIT TAKEN IMMEDIATELY AFTER INTRATRACHEAL INJECTION OF BLOOD AND TUBERCLE BACILLI

FIG. 2. FILM OF SAME ANIMAL AS THAT SHOWN IN FIGURE 1, THREE DAYS AFTER THE INJECTION OF BLOOD AND BACILLI

The shadow developed within 24 hours of the reinfection


1

2

General results

In none of the *normal* rabbits that were injected intratracheally with blood alone, or with suspensions of tubercle bacilli in salt solution or in blood, were acutely developing lesions demonstrable. In none of the normal rabbits, nor in any of the tuberculous rabbits that were injected intratracheally with blood alone, did changes develop that were comparable roentgenographically or anatomically to those found in some of the tuberculous rabbits that received intratracheal injections of suspensions of tubercle bacilli in blood.

see addn p 596

Specimen protocols

The protocols of several experiments are illustrative:

Sanguineous suspension of tubercle bacilli injected into the trachea of a tuberculous rabbit

Rabbit 22: May 5, 1925: Subcutaneous inoculation in the groin with bovine tubercle bacilli. *June 16, 1925:* Intratracheal injection, 2 cc. normal blood. X-ray examination of the chest on the succeeding three days showed nothing abnormal.

June 23, 1925: Intratracheal injection, 3 cc. of blood with tubercle bacilli. The X-ray film of the chest 24 hours after injection showed a new shadow of increased density in the lower lobe of the left lung. The shadow was about 1 x 0.75 cm. in diameter and, although uniformly dense, had ill-defined margins that faded gradually into the density of the surrounding tissue. It was the type of shadow interpreted usually as evidence of an anatomically recently formed lesion. Figure 2 is representative of this change.

Forty-eight hours after the second intratracheal injection, the animal was bled to death and autopsied. On the dorsal aspect of the left lung was an elevated area of consolidation; grayish brown, gelationous, about 2 cm. in its longest diameter, and with irregular margins. Toward the cephalic end of this area, as well as just to the left of its caudal end, were several small, depressed, pigmented spots, of a deep orange or chocolate color. The cut-section, viewed with the unaided eye, showed the pleural border of this solidified area to be elevated above the general surface of the lung and its mass lacked the open mesh-like appearance of the surrounding tissue.

Microscopically (figure 3), the pleura over the involved lung did not present the irregular wavy outline seen over normal lung, but was smooth as if it were tense. In the densely consolidated parts, the predominating cells within the alveolar spaces resembled epithelial cells, but they were less ovoid as a result of compression. In the area of less dense consolidation more elongated cells with eccentrically placed nuclei filled half or more of the individual alveoli. Numerous polymorphonuclear leucocytes were seen throughout the exudate. Red corpuscles, though present here and there, were less numerous than the color of the fresh specimen indicated they would be. Small accumulations of serum and of pigment were also seen. Throughout the area of exudation there were a few tubercle bacilli, singly or in small clumps, and generally intracellularly placed. The alveolar walls were slightly thickened and some of the capillaries were dilated.

Here and there throughout the remainder of the lung tubercles were seen, consisting of an outer zone of lymphocytes surrounding groups of large epithelioid cells, and often a central zone of necrosis. The peripheral collar of lymphocytes was thicker than is usually seen, and contained a few polymorphonuclear leucocytes and cells resembling epithelioid cells, but the perifocal inflammation around these lesions was not striking.

Sanguineous suspension of tubercle bacilli into the trachea of normal rabbits.

Rabbit 71: Normal: February 27, 1926: Intratracheal injection, 3 cc. of blood with tubercle bacilli. *February 28, 1926:* Roentgenograph of the lungs showed no new shadows. *March 1, 1926:* The rabbit was bled to death from the femoral artery.

Examination: The dorsal and lateral surfaces of both lungs were mottled with large areas of discoloration varying from a dark amber to chocolate. The areas were nowhere sharply demarcated, the surface was not elevated, and none was dense or indurated.

Microscopic examination of sections of such discolored portions of the lungs showed that the reaction to the blood was comparatively widespread (figure 4). Many alveoli contained

FIG. 3. LOW-POWER PHOTOMICROGRAPH OF A SECTION OF A LUNG, THROUGH AN AREA OF PNEUMONIC CONSOLIDATION SUCH AS THAT SHOWN IN THE FILM ILLUSTRATED IN FIGURE 2

Description is given in the text

red corpuscles or discolored serum, and in such areas there was atelectasis. The several small areas of bronchopneumonia that were seen were made up exclusively of small round cells and no polymorphonuclear or epithelioid cells were found. A few tubercle bacilli were seen in the alveolar walls, usually intracellularly placed.

Many of the normal rabbits that were given intratracheal injections of tubercle bacilli suspended in blood or in salt solution did not develop very extensive pulmonary tuberculosis. Others showed, after five or six weeks, massive tuberculosis of the lungs.

Rabbit 57: Normal: December 9, 1925: Intratracheal injection of 2 cc. of the standard suspension of tubercle bacilli in blood. Roentgenographs of the lungs made on December 10,

12 and 24 did not show any new shadows. A roentgenograph made on January 2, 1926, twenty-four days after the injection of tubercle bacilli, showed numerous irregularly rounded shadows throughout both lungs, and another examination made on January 14, 1926, thirty-six days after infection, showed the pulmonary fields densely mottled with confluent shadows (figure 5).

Necropsy on January 26, 1926, forty-eight days after infection: The lungs were voluminous. The pleural surface was irregular and lustreless; and pulmonary tissue was, for the most part, replaced by confluent areas of caseation and of gelatinous consolidation. There was no cavitation.

FIG. 4. LOW-POWER PHOTOMICROGRAPH OF SECTION FROM THE LUNG OF A NORMAL RABBIT THAT HAD RECEIVED AN INTRATRACHEAL INJECTION OF BLOOD AND BACILLI 48 HOURS EARLIER

THE REGRESSION OF SHADOWS AFTER INTRATRACHEAL INOCULATIONS OF TUBERCULOUS RABBITS

In several instances, serial roentgenographs taken at intervals for many days after suspensions of tubercle bacilli in blood had been injected into the trachea of tuberculous rabbits showed a disappearance of shadows

that had appeared promptly after reinfection, as in the following instances:

Rabbit 43: November 3, 1925: Subcutaneous inoculation in the groin with 0.1 cc. standard suspension of bovine tubercle bacilli. *December 28, 1925:* Intratracheal injection of 2 cc. of a suspension of tubercle bacilli in blood. Roentgenographs of the lungs made 24 hours after the intratracheal injection showed several shadows with ill-defined margins in the lower lobe of both

FIG. 5. ROENTGENOGRAPH OF A NORMAL RABBIT THAT HAD RECEIVED AN INTRATRACHEAL INJECTION OF BLOOD AND BACILLI 36 DAYS BEFORE

The evolution of the process was gradual, as serial films indicated

lungs. These shadows, evident first on the day after reinfection of the rabbit, were observed gradually to fade during the next six days, and on the sixteenth day after they were first demonstrable they had faded completely. *January 26, 1926:* Twenty-nine days after reinfection, the rabbit was killed; and examination of the lungs showed distortion of the right lung due to numerous tubercles scattered throughout the pleura and the parenchyma of the lung. Numerous small tubercles were present in the left lung.

Rabbit 51: November 3, 1925: Subcutaneous inoculation in the groin with 0.1 cc. standard suspension of bovine tubercle bacilli. *December 28, 1925:* Intratracheal injection of 2 cc. of a suspension of tubercle bacilli in blood. Roentgenographs of the lungs made twenty-four hours after the intratracheal injection showed several small shadows, with ill-defined margins, in the lower half of the right lung. These shadows decreased in size during the succeeding five days, became more sharply demarcated, and were still visible in films made on the 16th day after the reinfection. *April 6, 1926:* The animal was killed and at necropsy the lungs showed only a few tubercles undergoing caseation. No areas of organized pneumonia were found.

The roentgenographic mutations noted in these experiments suggest that an immediate exudative reaction developed when tubercle bacilli were introduced directly into the diseased lungs of tuberculous rabbits, and that, in some instances, this acute exudation was gradually removed. These changes simulate in kind those seen now and again clinically in a tuberculous patient after an haemoptysis has occurred.

DISCUSSION

In these experiments, the picture of widespread mottling of the pulmonary fields was not reproduced roentgenographically, in part perhaps because of the lack of technical finesse, in part perhaps because of the introduction of the blood under pressure. However, an acutely developing exudative reaction was demonstrated in tuberculous lungs when conditions were created that are analogous more or less to those that arise when an haemoptysis occurs in a tuberculous patient.

The nature of these pulmonary lesions that develop acutely after reinfection of the tuberculous animal is clear. The rabbits were sensitized because they were already infected; the lesion is a rapidly developing exudation of cells and serum identical with that which appears characteristically whenever there are new implantations of tubercle bacilli in an animal already tuberculous; the exudate may be absorbed spontaneously, just as is the collateral inflammation that develops about small foci of tubercle bacilli experimentally introduced into an infected animal. Finally, the failure of noninfected animals similarly to react, establishes the conclusion that the changes described are due to allergy and are not merely localized areas of bronchopneumonia similar to those described by Meltzer and Auer, by Blake and by others, following the injection of pyogenic cocci into the trachea.

On the basis of analogy, it is indicated that when, during or after an haemoptysis in tuberculous man, a few tubercle bacilli are introduced into the lungs, areas of collateral inflammation develop promptly about

the sites of reinfection because of the existing allergy. It is well known that often such acute inflammatory exudation gradually subsides and leaves as a residuum only a small central nidus that may contain a few viable bacilli. When the allergy is marked and the associated immunity is well developed, such areas of reaction may heal completely.

CONCLUSIONS

The foregoing evidence corroborates experimentally the idea advanced by Amberson on clinical grounds, that the disseminated cottony shadows or mottling seen occasionally in roentgenographs of tuberculous lungs, made promptly after an haemoptysis has occurred, are due in the main to this collateral exudation of allergy. As the acute reaction subsides, the mottling lessens and minute shadows caused by tubercles may be seen. Interpretation of the roentgenographic shadows based on these data justifies a more favorable prognosis than is usually made in the groups of cases under discussion.

THE INFLUENCE OF FREQUENTLY REPEATED REINFECTIONS ON ALLERGY AND IMMUNITY IN TUBERCULOSIS

An Experimental Study[1]

ALLEN K. KRAUSE AND HENRY STUART WILLIS

This paper relates attempts to reproduce experimentally conditions of tissue allergy and immunity to tuberculosis, which may be presumed to exist naturally in the body of the tuberculous animal, and attend the mobilization and focalization of those tubercle bacilli concerned in extensions and metastases of tuberculous processes.

By experimentation we find that tuberculous animals become allergic and immune by virtue of their tuberculosis. Both new properties are readily determinable upon the inoculation (reinfection) of such animals with living, virulent tubercle bacilli. Then their tissues undergo acute inflammation (allergic reaction) at places where bacilli focalize in sufficient numbers. If the bacilli are numerous enough, the animals will be made acutely, even fatally, ill by the reinfection. But, if they survive the illness which usually begins a few hours after the reinfection, they manifest their immunity by long outliving normal animals similarly inoculated with tubercle bacilli as of a first infection, or by displaying little, if any, tuberculosis due to their reinfection, at a time when the originally normal "controls" will have extensive and thoroughly generalized disease.

Tuberculo-immunity is found to be characterized, not so much by a capacity to ward off newly introduced bacilli completely, as to limit their activities within the body. Foci of reinfection, beginning acutely, soon settle down into chronic processes, with but little tendency to spread, or with extension noticeably retarded. They thus present a striking contrast to foci of first infection, set up by bacilli of equal virulence and quantity, which get under way leisurely and, with an appearance of irresistibility, lead to a condition of progressive tuberculosis.

[1] From the Kenneth Dows Tuberculosis Research Fund, of the Johns Hopkins Hospital and University.

Tuberculo-immunity must be a remarkably effective agent of resistance. There is every reason to believe that ten or fewer virulent bacilli, placed aright, will lead to progressive tuberculosis in the normal guinea pig. A tuberculous, and therefore immune, guinea pig will for months hold in check ten thousand times ten bacilli, and more, when these are introduced from without. The immunity of tuberculosis to a single reinfection from without may be *relative* as it is frequently called, but it is amazingly high.

Allergy and immunity to tuberculosis can be correlated at so many points that it is a fair inference that the one quality is a function of the other. There is much evidence to indicate that immunity is achieved through the tissue effects of allergy, as these are found to operate upon tubercle bacilli.

Allergy is a changeable property, fluctuating not a little during the ordinary course of an experimental infection, and modifiable by numerous incidents, specific to the infection and otherwise. In general, it rises with extension and increase of the infection and falls with the latter's subsidence, arrest and healing. It is usually stated that, in terminal tuberculosis, meningitis, generalized miliary disease, and extreme tuberculous cachexia, coincident with the general waning of the reactive powers of the body, tuberculo-allergy is *abolished*. This is quite likely an exaggeration; for the writer has never found tuberculous animals to be completely refractory allergically to tuberculin or tubercle bacilli. Moribund guinea pigs and others in wretched physical condition frequently fail to react to the ordinary applications of antigen; but, as the latter are increased, such animals always yield some noticeable response to sufficient quantities. This experience is in accord with observations made on human patients by Happ and Casparis (1). Infants and children (they found), in the last phases of generalized miliary tuberculosis, with and without meningitis and negative to Pirquet tests, practically always reacted positively to high enough concentrations of tuberculin injected intracutaneously.

The most that we can say, therefore, is that tuberculosis itself, as it brings about marked exhaustion of the bodily forces, *depresses* allergy and *exhausts* it also,—sometimes almost to the vanishing point. It exercises the same effect, though transitory and to a minor degree, during the few days of acute illness which follow the experimental reinfection of animals. This circumstance has its clinical analogue in the diminished skin reactivity exhibited by the patient in the early stages

of acute tuberculous pneumonia, a condition set up by the abrupt and fairly severe reinfection of the already tuberculous patient. Similarly, highly allergic guinea pigs will become much less hypersensitive to tuberculin and tubercle bacilli during the short period in which they may be laboring under a constitutional tuberculin reaction (2). On the other hand, single artificial reinfections very promptly and markedly raise the waning allergy of an experimental animal with old healing tuberculosis (2).

Accordingly, while tubercle bacilli in some unknown manner create the hypersensitive state, and serve to maintain it at a variable level, and with their proteins bring it into play by arousing the allergic reaction, tubercle bacilli and their proteins also *desensitize* or *anergize* tuberculous animals under the proper conditions of mass and time. It may be stated that, in general, the tissues of allergic animals are less hypersensitive, that is, less reactive to new contacts with specific antigen (tubercle bacilli and tuberculin), during that time in which the animals are undergoing allergic reactions of or above a certain intensity. What this intensity, this "certain intensity," need be we do not know. We cannot measure it, although we believe it is one that is marked enough to make some impression on the bodily economy,—enough, let us say, to lead to dysfunction and constitutional illness.

In this respect tissue allergy but follows a law that is universally applicable to immune substances. Specific precipitation, agglutination, complement binding, etc., are all transitorily depressed by repeated injections of antigen, spaced properly, only to rise to higher levels than formerly after the "negative phase" is recovered from.

Tissue tuberculo-allergy is affected by infections other than tuberculosis. The desensitizing influence of measles has been recognized since the days of our first knowledge of allergy, when it was noted by Pirquet. At the time of the great influenza epidemic of 1918–1919, Bloomfield and Mateer seized the opportunity to make Pirquet tests in 19 consecutive cases of influenza admitted to the wards of the Johns Hopkins Hospital (3). "Skin sensitiveness to tuberculin was absent in every case but one, both mild and severe, during the febrile stages. During convalescence reactivity returned in 89.4 per cent of the cases. . . . . The return to maximum reactivity was gradual in most cases, as shown by successive tests."

Such phenomena point to the fact that the intoxications (?) of at least some infectious diseases depress tissue hypersensitiveness. A

marked influence of measles in this respect may be suggestive. The semeiology of measles has enough of the earmarks of protein intoxication to allow speculation as to the probable part played by the latter in its manifestations. Measles and serum sickness are both without characteristic focalizing lesions. Both have a symptomatology of fever, eruptions, catarrh of the conjunctiva and upper air passages, adenitis, and other minor manifestations. Indeed, uncomplicated influenza, when marked by erythema, can present features to make one think that a protein intoxication may be responsible for its symptomatology. We would not push the point too far. But we would remark, in passing, that if protein intoxication were, in fact, responsible for the symptoms of measles, we could more readily understand why measles is (of all infections) unusually desensitizing for tuberculo-allergy.

The physiological disturbance of pregnancy is said to reduce the allergy of tuberculosis. This association deserves much more extensive study than has thus far been reported, in order that variable factors may be more accurately appraised. We have observed an undeniable and marked depression of skin sensitiveness in pregnant and parturient tuberculous guinea pigs, but have not studied the effects of pregnancy systematically. The influence of such exhausting conditions as fatigue and anaemia and malnutrition on allergy should be carefully investigated.

It is not particularly difficult to prove that tissue tuberculo-allergy is affected by a number of circumstances that enter into ordinary experience, including the varying specific influence of tuberculous foci themselves, as the character of these changes from time to time and, consequently, the relations between tubercle bacilli and the body which harbors them also change. All that is required is careful observation of the results of repeated tuberculin tests; and guinea pigs lend themselves admirably to this purpose.

But the satisfactory determination of changes and modifications of immunity is not nearly so simple. Technical difficulties stand in the way of the scientific demonstration of the most fundamental and most crucial of all the problems of tuberculo-immunity; namely, its relation to tuberculo-allergy. As mentioned above, there is ample evidence that such a relationship exists. But most of the evidence is indirect, and based on the almost invariable concomitance of the two phenomena and on their similar modifications in the same circumstances. For

instance, measles, influenza and pregnancy, which depress tuberculo-allergy, have been especially noticeable as activators of tuberculosis; that is, as presumptively reducing resistance to infection previously held better in check. As nearly as can be determined by experiment, the conditions necessary for the initiation, intensification, diminution and termination of tuberculo-allergy and immunity appear to be the same. (And it may be mentioned that such an association does not hold as between tuberculo-immunity and any other so called "immune process,"—precipitation, agglutination, etc.)

Again, as has frequently been shown in publications from the Kenneth Dows Laboratory,[2] the direct effect of the allergic reaction may be conceived of as being of such a kind as to oppose the spread of tubercle bacilli within the body, and thus achieve a result comprehended by us as immunity. Obviously, the scientific proof of such an hypothesis hinges on the possibility of reducing immunity by actively diminishing or wiping out allergy. If it could be shown beyond question that desensitization or anergization is attended by specifically lowered resistance to tuberculosis, it would appear that the function of allergy as an agent of increased resistance would be established.

For over fifteen years the writer has been engaged in attempts to alter (reduce) tuberculo-immunity and allergy by protein intoxication. The published results to date may be summarized as follows:

1: Reported by Krause, 1911 (4): Nontuberculous guinea pigs were *anaphylactically* sensitized with tuberculoprotein (water extract of dried, pulverized tubercle bacilli). They were put in a state of nonfatal anaphylactic shock by toxic injections of tuberculoprotein. While still markedly ill with anaphylaxis they were inoculated with virulent tubercle bacilli. They developed tuberculosis to an extent to justify the conclusion that "resistance to infection is markedly lowered during the period that a sensitized animal is suffering from symptoms of anaphylactic shock."

Note: In these animals *tissue* allergy did not come into question. While nontuberculous they were rendered very ill by specific means—by tuberculoprotein—and, while still quite sick from *general* protein intoxication, were infected for the first time. The main deduction to be drawn is that during

[2] For a summary of this work the reader is referred to *Appendix A: Remarks on conditions necessary to arouse the allergic state and on immunity through fixation of bacteria, Amer. Rev. Tuberc., 1925, xi, 343,* subjoined to *Human resistance to tuberculosis at various ages of life,* Ibid., 1925, xi, 303. The appendix is also published as a separate paper in *Tubercle, 1925, vii, 29.*

illness from tuberculoprotein (that is, specific) intoxication, an animal (nontuberculous and nonimmune) is rendered more open to tuberculous infection. Among clinical analogues that at once suggest themselves is the case of the patient in the first flush of acute tuberculous pneumonia,—laboring under the constitutional symptoms of his tuberculo-intoxication and at the same time exposed to repeated new focalizations of bacilli mobilized from old parent foci. Is such a patient in unusual danger from superinfection during the period of his intoxication? But, only a moment's reflection will show that the cases of the nontuberculous anaphylactic guinea pig and the specifically intoxicated tuberculous patient, similar in respect to intoxication and exposure to infection, are in other significant relations quite different. At the time of its infection, the tissues of the guinea pig were nonallergic because it was nontuberculous: at the time of his superinfection, the patient's case is complicated by the presence of allergy, modified though this might be, and by a specific immunity as well. Nevertheless, the experiment cited clears the problem to the extent that it indicates that, acting by itself and unopposed by other checks or balances (such as an immunity in being), specific protein intoxication to the point of marked illness reduces resistance for the time being.

2: Reported by Krause, 1916 (5): First, guinea pigs were sensitized, *while nontuberculous,* with tuberculoprotein (water extract). They were then thrown into anaphylactic shock and, immediately afterward and while still ill, were inoculated with living R1 tubercle bacilli, germs of low and nonprogressive virulence. The *result* was not decisive enough to indicate that the "invasiveness" of these slightly virulent bacilli had been increased,—in other words, that resistance was appreciably reduced in such a way that bacilli could exhibit new qualities of virulence.

Second, guinea pigs were first sensitized anaphylactically with tuberculoprotein, and then *infected* with R1 bacilli, and intoxicated by a single anaphylactic shock *after* infection. The *result* indicated that "a single attack of anaphylaxis [during the evolution of tuberculosis] does not bring about an extension of the disease."

Third, the pathogenic effects of a saprophytic acid-fast bacillus (Moeller's Mist bacillus) were not enhanced by methods similar to the above.

Note: These efforts to reduce resistance were made with germs of little or no virulence put into soil affected by single and transitory periods of specific protein intoxication. In the second instance, tubercle bacilli were in the body before the beginning of anaphylactic shock, and had been there for over seven weeks. Relations were therefore more comparable to those in the tuberculous patient who may suffer from specific protein intoxication. It was stated at the time that "if, after infection was once established, an animal could be kept in a more or less continually intoxicated condition (that is, anaphylactic intoxication) perhaps the result would be different."

3: Reported by Krause, 1916 (2): Nineteen tuberculous guinea pigs reacted with great vigor to skin tests. Seventy-two hours after the intracutaneous injections of tuberculin, which caused the skin reactions, they were given water-extract intraperitoneally. During the following night 3 died from the resulting constitutional reaction, while several of the survivors were found to be very ill the next morning. At this time a few of the stronger ones were again tested intracutaneously. In one, which died two days later, no reaction occurred, while in the others the reactions were much reduced and were much more fleeting.

Note: The result was definite. Tissue allergy is depressed during the period of intoxication of the constitutional reaction. But the experiment also threw out hints of technical difficulties ahead. It suggested that, if we were to diminish allergy markedly (and, therefore, immunity, if our hypothesis were sound), we should quite likely be obliged to intoxicate our animals almost to the point of death. Such a contingency would, of course, render impossible a study of immunity, which requires weeks and months of controlled observation for its proper interpretation.

4: Reported by Krause and Willis, 1919 (6): This report recited several experiments, the leading object of which was to observe the effects on tuberculous infection of frequently repeated applications of both homologous and heterologous protein, which, it was hoped, would lead to chronic intoxication of the animals.

First, during almost four months guinea pigs received, *while nontuberculous*, a total of 85 intraperitoneal injections of tuberculoprotein (water-extract), for a gross amount of 203 cc. They were then inoculated with virulent tubercle bacilli. Coincidently, other nontuberculous guinea pigs received 70 injections of egg-white, for a total of 120 cc., and were then similarly infected. *Result:* "The evidence though far from decisive points to the probability that frequent injections of protein over a long period of time render an animal abnormally susceptible to tuberculous infection."

Note: The frequently repeated injections of protein (five to six times a week) did not render the guinea pigs manifestly ill. It cannot, therefore, be said that we gained our objective,—a state of chronic intoxication. On the whole, the results, as regards an influence on infection, must be considered as quite inconclusive.

Second, guinea pigs were first infected with R1 tubercle bacilli, and then subjected to injections of egg-white, five or six times weekly, for almost three months,—for a total of 85 cc. in 58 injections. *Result:* No appreciable influence on infection.

Note: Again the animals failed to display symptoms of intoxication, and again we were unsuccessful in putting guinea pigs in such a state of lowered

resistance that bacilli of slight virulence would "take hold" to more than usual effect.

Third, guinea pigs were first sensitized with egg-white (single initial injection). Two days later they were infected with *R1.* At from twenty to twenty-two days after sensitization they were precipitated into anaphylactic shock with large doses of egg-white, and then, for approximately six weeks more, were treated similarly every four to ten days. After the third injection all animals became refractory to egg-white, in that they no longer showed symptome of anaphylaxis. *Result:* The R1 infection was not appreciably influenced.

Note: The object of the experiment was not fulfilled, inasmuch as we failed to produce frequent enough acute intoxications of the infected animals.

Fourth, those animals (nontuberculous), which had received almost daily injections of tuberculoprotein for four months, never gave positive skin reactions to tuberculin until they were infected later,—a further confirmation of the generally accepted view that infection (tubercle) is necessary to the creation of tissue allergy.

Fifth, the repeated application of heterologous protein (egg-white) to tuberculous guinea pigs had no effect on the tissue allergy of the latter to tuberculoprotein.

5: Reported by Krause and Willis, 1920 (7): The problem of the relation between tissue allergy and immunity was now approached from another angle.

The skin of tuberculous guinea pigs was made to react vigorously to intracutaneous injections of tuberculin. Virulent tubercle bacilli were then inoculated into such reacting areas at variable intervals (one, two and four days) after the reactions had begun.

Results: Both tissue allergy and immunity were reduced during the period of acute allergic reaction at the site of reaction. The diminution was more marked during the first day or two of the acute reaction than later (at four days) when the reaction was subsiding. In no case, however, was the reduction of allergy and immunity complete, to the point of abolition.

Note: This experiment indicated that, *after* a tissue allergic reaction is set in motion, the site of reaction is a local point of less than standard allergy and immunity for the animal, for a period that probably comprises that of the acute inflammatory phase of the reaction.

The leading features of allergy and immunity, which were learned from the experiments just outlined and which were to guide us in future experimentation were as follows:

1. Heterologous protein intoxication before tuberculous infection probably affects tuberculo-immunity adversely.

2. Homologous protein intoxication (that is, with tuberculin) before infection quite likely does so.

3. Homologous protein intoxication (with tuberculin) depresses tissue allergy in tuberculosis.

4. Frequently repeated injections of heterologous protein did not reduce tuberculo-allergy; but it must be observed that a condition of appreciable chronic intoxication was not thus attained.

5. For a short time an area of allergic tissue reaction is a site of diminished local allergy and immunity to freshly focalizing bacilli.

6. It is probable that satisfactory and decisive evidence of the effects of diminished allergy on immunity can be had only from animals which are kept for a long time in a state of severe intoxication, although to arrive at these conditions might jeopardize the success of any experiment because of premature deaths of animals.

The method of biological experimentation, as applied to tuberculosis, can present no more brilliant achievement than the laborious accumulation of the evidence that led to the formulation of the principles of tuberculo-immunity. So deceptive are the manifestations of the *Klinik* of tuberculosis that, as we may remember, tuberculosis was long exemplified as lying outside the common run of infectious diseases; it was called upon to illustrate, as a classical type, those infections into whose manifold operations no elements of real immunity, of specifically increased resistance to bacillary localization, entered. It was only planned experiment, with its controlled and intentional elimination of irrelevant and spurious phenomena, that could possibly have overturned this opinion.

But, it is is none the less true that having, with the instruments of the laboratory, reduced tuberculo-immunity to clear-cut and simple terms, we are still far from elucidating the effects, immediate or remote, which this immunity shall have on the course of established tuberculosis in animals or man. In the short period since its scientific incarnation tuberculo-immunity has been dignified by a body of literature that is above the average in both mass and quality. Haste and enthusiasm and a certain ingenuity (as well as frequently ignorance) have marked the innumerable attempts to apply the facts of experiment to the perennial puzzles of human tuberculosis, and lay these bare; yet it is doubtful whether, in a single instance an experiment on tuberculo-immunity has been conducted under conditions remotely approximating those

which must obtain in the course of ordinary human infection. This stricture can fairly be made even in regard to the most satisfactory and illuminating work on immunity to tuberculosis that has thus far been performed; that is, the exhaustive observations required in the years of trial of active immunization of cattle. Perfectly proper for their own purpose, that is, for specific prophylaxis, no studies of immunity in cattle proceeded along lines which were designed to simulate artificially those conditions of immunity which tubercle within the body must be expected to encounter.

Our basic facts of immunity have all been acquired through relatively elementary procedures; and they are, no doubt, all the more firmly established because of the uncomplicated methods employed. Susceptible animals have been given limited foci of tubercle and, after a proper interval, have been found to be over-resistant to more virulent superinfection. As time went on, successive tests or single tests at lengthening intervals would disclose the permanence or the changing competence of immunity. Or, several prophylactic inoculations would show whether a higher or more lasting immunity was to be gained than after a single infection. With very rare exceptions, tests of resistance have always been made at those intervals after preventive inoculation when immunity was known to be high.

Accordingly, the bodies of animals of experiment, in which it was desired to create immunity, have almost always been subjected to the influence of tubercle bacilli only once, or a very few times at carefully and intelligently spaced intervals; and since, from the requirements of the case, only germs of low virulence were used,[3] we may presume that these have always been soon well arrested, and rendered incapable of making many or significant excursions into new soil. Under the circumstances, it must have resulted that newly introduced bacilli always struck contact with highly immune tissues.

It is self-evident that, in the body of the tuberculous animal or patient, the relations to tissue allergy and immunity of those bacilli which emerge from foci that can have any pretensions to activity and progressiveness must often be entirely different from these encountered by the "test bacilli" in the artificially immunized animal. Let us suppose that, as frequently happens, a focus is poorly invested, or that it breaks through and communicates with a channel of discharge and dissemination,

[3] That is, except for the more virulent inoculations applied to test the degree of immunity.

events that are part of the natural history of perhaps every really active case of tuberculosis,—certainly of every case in which foci come into view and extend and multiply. Such foci now become *more or less* continuous "feeders" of bacilli into allergic and immune tissues. We cannot, of course, tell whether fresh localizations will take place every few minutes, or hourly or monthly. But we can be certain that they will not be spaced so intelligently and so favorably as to fall at just those intervals that fit in with the highest levels of immunity.

If they crowd upon each other, and involve adequate numbers of bacilli, we must, according to all our knowledge of immune processes, expect to find happen a reduction of allergy and immunity, and an intoxication, and the latter, in turn, reacting unfavorably on allergy and immunity. Until the terminal cachetic stages of disease are reached, we would also predict that, whenever a material lessening of bacilli occurs or a lengthening out of the intervals between their successive exits from foci, a sharp recuperation of both allergy and immunity, perhaps to new high levels, will occur. Our experiments, performed thus far and cited above, would lead us to believe that, under no circumstances except perhaps in the most extreme intoxication and with death imminent, will animals have their allergy or immunity wiped out. Either or both may be very low; but, in some measure, however slight, they will be in existence, whereas the animal without tubercle will possess neither. If this is sound reasoning, then logic will compel the further inference that, with the reservations just suggested, almost the sickest tuberculous animal is favored with a modicum, a residuum, of allergy and immunity which the nontuberculous animal cannot enjoy,—again with the added reservation that, for the shortest time (measured perhaps in minutes) after the localization of adequate numbers of bacilli, both allergy and immunity may be abolished, and resistance sent to levels below that of the normal animal. We must always take account of the enormous powers of recuperation that characterize immunity processes, as long as any vestige of such powers remains. While this last reservation has eluded direct proof, we have had some evidence to suggest it.

EXPERIMENTS

Bearing in mind our past studies, as well as considerations similar to the foregoing, we approached the problem anew with experiments designed to modify tuberculo-allergy and immunity, if possible, by sub-

jecting guinea pigs to long-continued daily inoculations of living tubercle bacilli.

The experiments were conducted during the greater part of three years. They fall naturally into two parts. In *Part I* tubercle bacilli R1, of low virulence, were employed in the daily reinfections. In *Part II* the germ used for this purpose was the more virulent H37.

Part I: Daily reinfections with R1, tubercle bacilli of low virulence[4]

General outline of plan and procedure

Preliminary sensitization and immunization: With living R1 bacilli.

Repeated reinfection: Daily, with R1 bacilli.

Method of reinfection: Some guinea pigs intracutaneously; some subcutaneously.

Decisive inoculation to test effect on immunity: With virulent H37 bacilli.

Information expected: The influence of frequently repeated reinfections on tissue allergy; whether this influence, if demonstrated, was variable, according as "dosage" of reinfection was small or large; whether immunity was modifiable, by daily reinfection, to an extent that R1 bacilli could cause generalized disease instead of its customary self-limited infection following single subcutaneous inoculation or several spaced subcutaneous inoculations; whether daily R1 reinfections would bring about noticeable and chronic intoxication in originally immune animals; whether H37 virulent infection would set up more or less disease than usual in such guinea pigs, if chronic intoxication occurred.

Experiment A: Sensitization and immunization

Twelve normal guinea pigs were inoculated subcutaneously, each with 0.5 cc. of a heavy suspension of R1 bacilli in physiological salt solution. Ample experience had taught us that such inoculations lead to no visceral tuberculosis, cause palpable infection of the regional lymph nodes and usually noticeable changes in the tracheobronchial lymph nodes, and render the subjects for a long time both hypersensitive to tuberculin and tubercle bacilli, and highly immune to more virulent bacilli.

[4] The results of Part I have been published in abstract under the title, *The effect of frequently repeated reinfection on allergy and immunity to tuberculosis in guinea pigs, Trans. Assoc. Amer. Phys., 1924, xxxix, 86.*

Experiment A: Daily inoculations with R1 bacilli

Exactly three months later, and without having had any further treatment in the meantime, the 12 guinea pigs were divided into two lots of 6 each. The members of lot 1 were, from now on, to receive daily *intracutaneous* inoculations of living R1 bacilli, and those of lot 2 daily *subcutaneous* inoculations. This would mean that the daily reinfections of lot 1 were made with relatively few bacilli, and of lot 2 with comparatively large numbers. Fresh suspensions of living R1 were to be made daily from cultures. Those for intracutaneous inoculations were to be moderately thin, filtered after centrifugation, and showing roughly 15 to 25 bacilli to the oil-immersion field, and daily dosage to be 0.1 cc. The suspensions for subcutaneous inoculation were to be moderately heavy, and daily dosage 0.5 cc.

1: Further course of lot 1: With the lapse of time the results in these animals exceeded all expectations. *Every one of the 6 guinea pigs received a total of 86 daily reinfections with living R1 intracutaneously.* With the exception of some loss of muscular tone, which will be mentioned later, all the animals remained in excellent physical condition throughout the period of daily infections. When it is considered that these guinea pigs, for almost three months, lived with the greater part of their body shaved and with upward of a half-dozen skin reactions always in various stages of evolution, the result is truly amazing. It is also believed that these animals and their original fellows, now of lot 2, experienced the most intensive and unremitting contact with living tubercle bacilli ever recorded for animals of experiment.

The almost complete record of tissue allergy under such conditions is unfolded graphically in the series of drawings pictured in figures 1 to 10 on plates 1 to 4. These are drawings of the same animal, carried through 80 daily skin reactions to *living* bacilli. They are about half natural size, and the animal is representative of the lot.

Figure 1 presents the results of the first six daily skin infections. It was drawn twenty-four hours after the sixth or last of these inoculations. It therefore shows the allergic reactions as these appeared at 24 hours after the sixth, 48 hours after the fifth, 3 days after the fourth intracutaneous reinfection, and so on. It can be seen that during the first week of skin infections allergy was very high, and the allergic reaction correspondingly vigorous. Here, at twenty-four hours after the sixth reinfection, its site is occupied by a large area of redness and indura-

tion, with haemorrhagic necrosis already marked in its centre. At forty-eight hours the reaction of the fifth reinoculation is subsiding somewhat. The site of first reaction, now six days old, is scabbing over and healing. All in all, vigor, intensity and speed characterize the tissue responses to these early infections. The animals meanwhile do not show the least ill effects constitutionally.

In the second week (fig. 2) there began to be some delay in the evolution of the skin reactions. They were not so prominent at twenty-four hours, and the maximum effect was now more likely to be postponed to forty-eight hours after infection. Necrosis appeared a good deal later than during the first week.

This reduction of reactivity was still more pronounced in the third week (fig. 3). Redness and induration became less marked, and necrosis much less so. A comparison of figure 1 with figure 3 will show how much the original allergy had declined. As a matter of fact, we learned that from about the twentieth to thirtieth days of repeated reinfection we could always look for a marked depression of allergy, if depression was to occur.

Through the fourth and fifth weeks reactivity did not appear to change greatly. It was sometimes greater and sometimes less, with, if anything, a net reduction by the end of the fifth week. This reduction continued and became still more noticeable in the sixth and seventh weeks. Sometimes there was only the slightest necrosis; at other times, no necrosis whatever. (See figs. 4, 5 and 6.) Meanwhile the animals were showing some constitutional effects of the infections, for it was noted, from time to time, that they were lax and somewhat listless. Yet, in view of their treatment, they seemed to be in remarkably good condition.

In the eighth week there appeared a change for the better. Reactivity was again "picking up," and the increase was especially noticeable at twenty-four hours (see fig. 7). At the time of the fiftieth inoculation, it was noted that the animals had been livelier for the past week and had been making appreciable gains in weight.

The animals were still reacting well in the ninth and tenth weeks, but again not so well in the eleventh week (figs. 8 to 10). However, they kept in very good condition; and on the eighty-second day it was noted that reactions were again prominent.

As has been stated, the daily reinfections were terminated on the eighty-sixth day. At this time the animals were lively, and their general condition seemed to be normal in every way. After the almost three

months of daily reinfections they had not lost weight, which was about the same at the end as at the beginning of the repeated reinoculations. They were now infected *subcutaneously* with large "doses" of virulent bacilli, and placed with other guinea pigs, to be carried along as subjects of *Experiment B*, to be described below.

Remarks and summary: The foregoing experiment provided the opportunity to observe the effects on tissue allergy of closely repeated reinfections over a long period of time, and under conditions which it is all-important to keep in mind. These conditions, which no doubt play their part in shaping the outcome, were: (1) the germ used was of low virulence; (2) the "dosage" was always relatively small; and (3) the site of localization was always the skin.

Under these circumstances tissue allergy is reduced. Although daily reinfections are kept up for almost three months, the allergy is never abolished; indeed, a good degree of it is retained at all times. It is in about the third or fourth week that we can look for a marked depression of allergy, although, quite likely, some diminution takes place from the beginning. Although no change is made in the treatment of the animal, for unknown reasons allergy fluctuates from time to time within minor limits. The animals keep in good physical condition, and show

DESCRIPTION OF FIGURES

A guinea pig, originally immunized (sensitized) with living R1, and then given successive daily intracutaneous inoculations over a period of 86 days. Drawings are about half natural size. See pp. 328–329 of text.

FIG. 1. The results of the first 6 repeated intracutaneous inoculations. Drawn 24 hours after the 6th or last inoculation. Therefore shows the reactions as these appeared 24 hours after the 6th, two days after the 5th three days after the 4th intracutaneous inoculation, and so on.

Skin sensitiveness at the end of the first week of daily reinfections is very marked, as appears from the very vigorous reaction at the site of the 6th inoculation. Here, 24 hours after the inoculation, is a large area of redness and induration, in which haemorrhagic necrosis has already taken place. The reaction due to the 5th inoculation is subsiding a little. That due to the first is scabbing over and healing.

FIG. 2. The results of the 9th to 14th daily inoculations. The drawing made 24 hours after the last, or 14th infection.

By the beginning of the second week the reactions were becoming delayed in appearance. They were not so prominent as during the first week at 24 hours after inoculation, and the acme of reaction was sometimes postponed to 48 hours after infection. Necrosis was less, and was markedly delayed. Redness and induration were also less marked.

FIG. 3. Results of the 17th to 23rd infections. Drawn 24 hours after the 23rd inoculation.

The animal is now in the third and fourth weeks of daily inoculations. Reactivity is still declining. It is at about this time that a definite and often very pronounced diminution of reacting capacity is always to be made out.

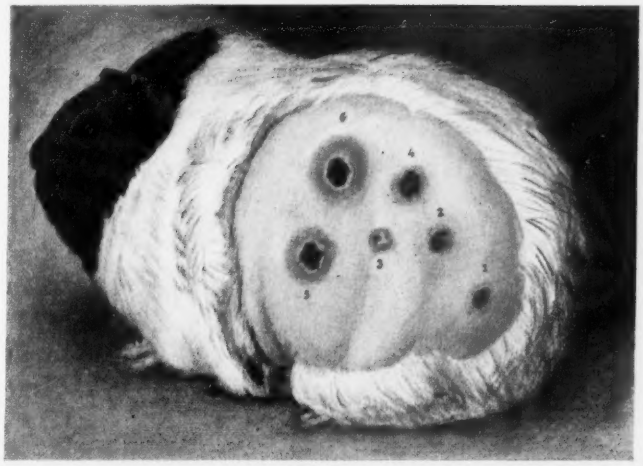


FIG. 1

FIG. 2

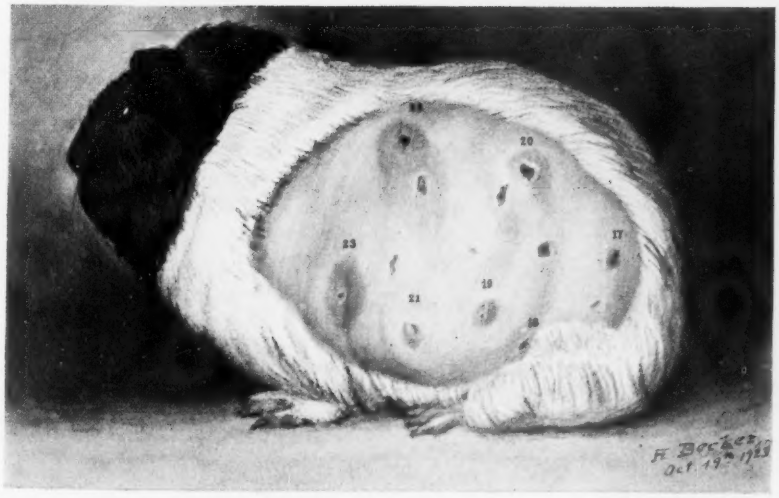


FIG. 3

FIG. 4. Results of the 25th to 31st infections. Drawn 24 hours after the 31st inoculation. The animal is in the fourth and fifth weeks of daily inoculations. If anything, it is reacting slightly better than the week before. At this time the notes of the experiment record that all animals have been lax in muscular tone for some time.

FIG. 5. Results of the 35th to 40th infections. Drawn 24 hours after the 40th inoculation. The animal is now in the sixth week of daily inoculations. Reactivity is much reduced.

FIG. 6. Results of the 42nd to 47th infections. Drawn 24 hours after the 47th inoculation. Now in the seventh week of daily inoculations. Reactivity is markedly reduced. Sometimes only the slightest necrosis occurs, or there is none whatever.

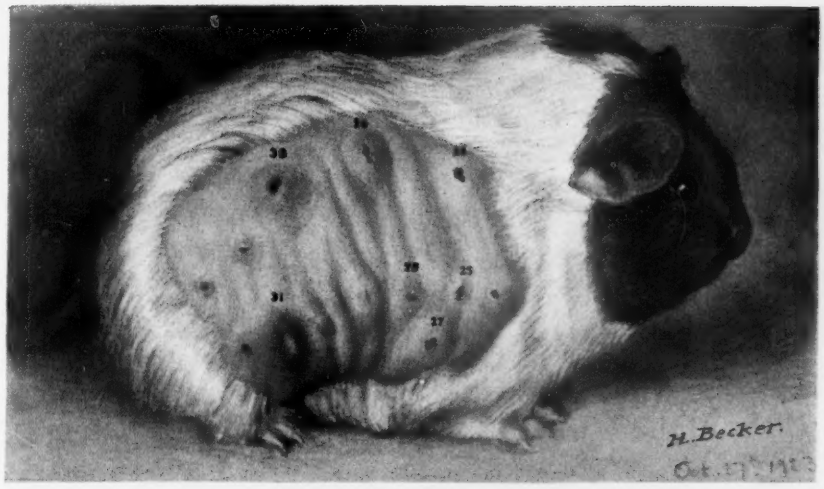


FIG. 4

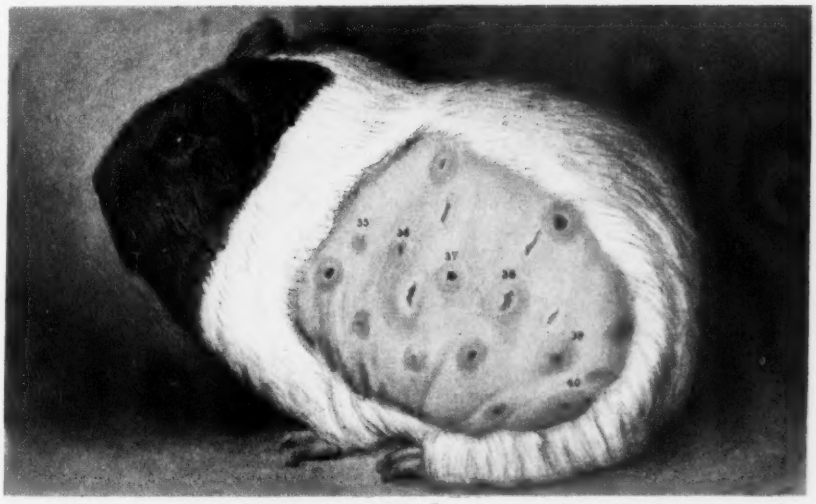


FIG. 5

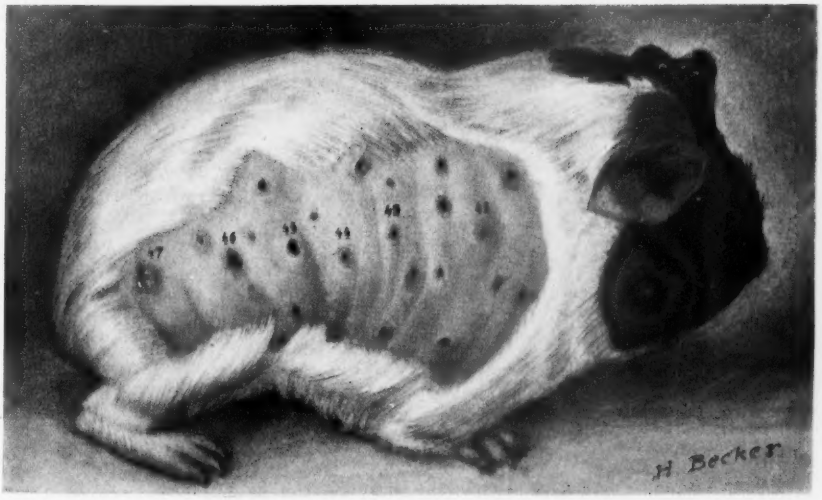


FIG. 6

FIG. 7. Results of the 48th to 54th infections. Drawn 24 hours after the 54th inoculation.

In the eighth week of daily inoculations. At this time the notes of the experiment record a tendency to increased reactivity in all animals. Suggestions of this are also to be made out in the illustration, which shows larger areas of reaction and more pronounced necrosis than does figure 6. The increasing reactivity was more noticeable at the twenty-four hour readings than later. It is also recorded, at the time of the 50th inoculation, that for a week past the animals had been acting more lively, and that they had gained appreciably in weight.

FIG. 8. The results of the 55th to 61st infections. Drawn 24 hours after the 61st inoculation.

Now in the ninth week of daily inoculations. The animals are still reacting well.

FIG. 9. The results of the 62nd to 68th infections. Drawn 24 hours after the 68th inoculation.

In the tenth week of daily inoculations. The reactions are again becoming more feeble, but the animals are keeping in good condition.

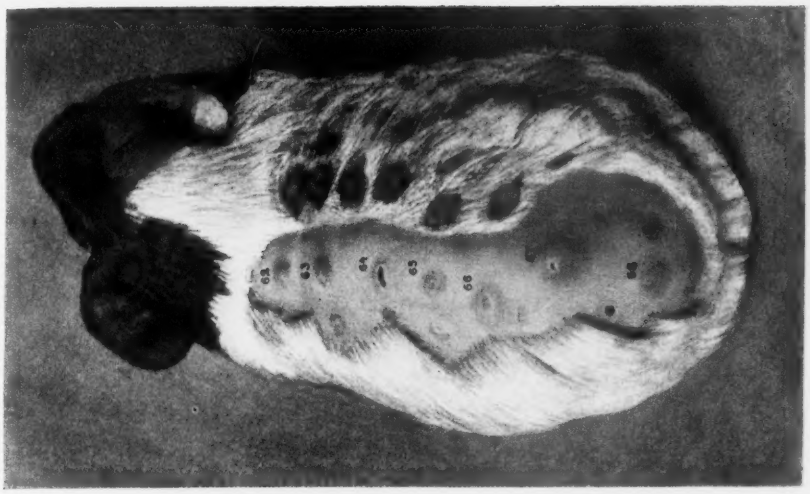


FIG. 9

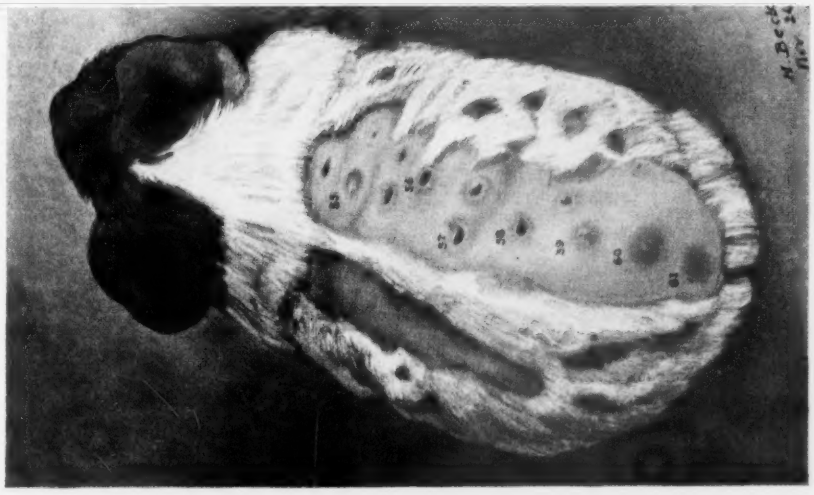


FIG. 8

FIG. 7

FIG. 10. The results of the 69th to 80th infections. Drawn 24 hours after the 80th inoculation.

In the eleventh and twelfth weeks of daily inoculations. The reactions are not vigorous.

On the 82nd day it was noted that the reactions were again becoming more prominent.

On the 86th day the daily inoculations were terminated, and the animals were inoculated subcutaneousiy with large "doses" of virulent human tubercle bacilli.

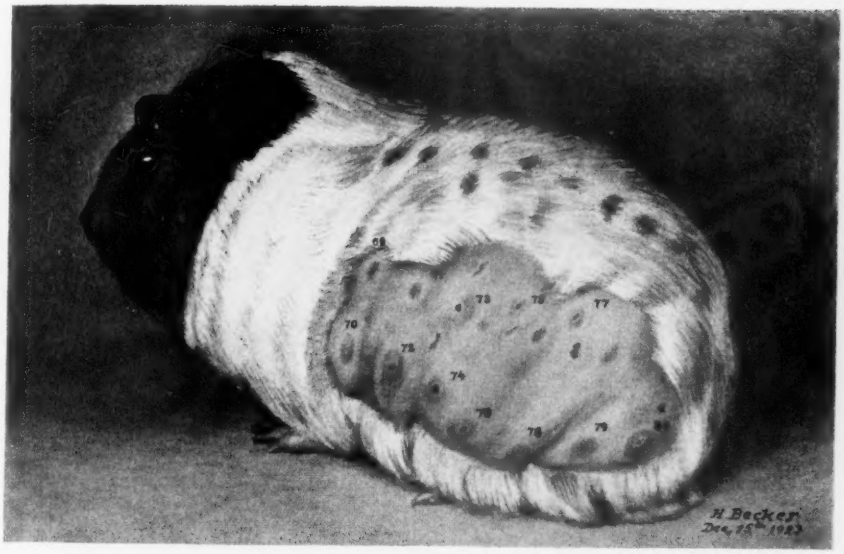


FIG. 10

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only slight evidences of intoxication. All in all, to judge from this single experiment, one becomes impressed with the large numbers of bacilli probably necessary to affect allergy profoundly, or to bring about great intoxication in the case of extension or metastasis of the disease.

2: Further course of lot 2: The members of this lot were the animals which received large numbers of living R1 *subcutaneously*. They were treated in this manner *for 68 successive days*. During this time their tissue allergy was tested nine times by means of intracutaneous injections of *tuberculin;* that is, skin tests were made about once a week.

A marked influence on allergy was noticeable almost immediately. At six days, the time of the first intracutaneous tests, the skin reactions were very slight, and fleeting as well; and, in general, this low reactivity continued during the period of daily reinfections. Now and then there would be fluctuations, when reactions were more vigorous for a time. The point of lowest allergy seemed to have been reached at about the fourth week, while at six weeks fairly vigorous reactions were again noticed.

Toward the end of the third week abscesses began to form, and with time this tendency became marked. Indeed, during the second half of the experiment the general involvement of the subcutaneous tissue with multiple collections of pus, which would develop rapidly after every reinfection, was the most marked feature in the animals. Never have we seen a better example of suppuration as an end-result of the allergic reaction in tuberculosis than in these animals.

Yet, the animals continued in surprisingly good physical condition. They were manifestly more affected, as shown by their lethargy and loss of muscular tone, than the guinea pigs of lot 1. But they were not strikingly ill, and finished the experiment as heavy as when they entered upon it.

On the sixty-ninth day, twenty-four hours after having had the sixty-eighth daily inoculation, the guinea pigs were killed, and examined postmortem. All had the superficial subcutaneous abscesses which have been mentioned. *There was no focal tuberculosis in the viscera of any animal.* The well-preserved body and visceral fat was noteworthy. An unexpected finding was the presence of a *plastic peritonitis in every animal,* while in several there was also plastic pleuritis in addition. With no appearance of focal tubercle, the abdominal viscera,—liver, spleen, etc.,—were adherent to the peritoneum. This condition of chronic peritonitis (and pleuritis) without visceral tubercle was identical

with that designated in human beings as *polyorrhomenitis* or *polyserositis*. The causes of its origin in the present instances are obscure. It is certain that no faulty inoculations were made directly into the abdomen or thorax. We may wonder whether the abnormal anatomical relations, which must have resulted from widespread suppurative involvement and induration of the subcutaneous tissue, led to the conveyance of bacilli along unusual and collateral circuitous paths (lymphatics?) to the peritoneum and pleura. The interesting, and perhaps significant, feature is that the pathological changes noted should have occurred under conditions which provided the long-continued "feeding" of bacilli of low virulence to the tissues of immune animals.

Remarks and summary: From almost the very beginning of the infections with large "doses" of living bacilli of low virulence, allergy went to a very low level, where it remained without being abolished, throughout the experiment, yet now and then increasing markedly for a while. The guinea pigs suffered less from intoxication than had been anticipated. But, there developed two conditions to account for this; and they may also serve to illustrate how complicated the contingencies of experiments of this nature may become. In the first place, the extraordinary number of inoculations made necessary the employment of every available spot of the subcutaneous tissue for infection. Because of the reactions and induration that followed the infections, it must have happened that the natural avenues of absorption were soon pretty thoroughly blocked. At the same time, as the abscesses ruptured, much, if not most, of the pus was discharged to the outside. It is therefore doubtful whether, especially during the second half of the experiment, the animals could have absorbed much, either in the way of bacilli or pus.

Significant again was our failure to alter resistance to an extent that R1 bacilli would "take hold," and cause progressive tuberculosis. Yet, in view of what has just been said, we must again ask ourselves whether many bacilli were carried into the body after the first few infections, when resulting reactions began to block lymphatic paths. *Perhaps* it was the long-continued and rather constant settling of *few* bacilli in low-allergic soil which "set the stage" for polyorrhomenitis; and in this connection it may be pertinent to recall that slight hypersensitiveness is a common clinical feature of tuberculosis of the serous membranes.

3: Late results of daily reinfection with R1: After preliminary sensitization and immunization (subcutaneous) with R1, other guinea pigs

were given 51 successive daily subcutaneous inoculations with living R1 bacilli. The immediately observed effects were similar to those described above in the members of lot 2. They were then allowed to live on indefinitely in the laboratory. When killed at intervals, and examined postmortem, they were never found to have visceral tuberculosis up to more than a year after the cessation of daily reinfections.

Experiment B: The influence of repeated reinfections of R1 on immunity

In this experiment guinea pigs were given single heavy inoculations with virulent H37 bacilli after they had been first sensitized and immunized; and, when immune, they were subjected to daily infections with R1 bacilli over a long period.

The animals used in this experiment were as follows:

Lot 1: Those guinea pigs which had been included in lot 1 of *Experiment A*, and had received 86 successive daily intracutaneous infections with R1.

Lot 2: Guinea pigs, which had first been immunized (and sensitized) with R1, and had then had 51 successive daily inoculations with R1 *subcutaneously*. During this time their allergy was greatly depressed, and they suffered from appreciable chronic intoxication, as well as many subcutaneous foci of suppuration.

Lot 3: Guinea pigs, which had received a *single* subcutaneous inoculation of R1, which was to immunize them against the H37 inoculation of the experiment. These animals served as the controls as to immunity. The effects of H37 in them could be considered as the standard of infection set up by H37 in the animal known to be immune.

Lot 4: Normal, nonimmune guinea pigs. These were the controls to indicate the involvement caused by H37 in nonimmune animals, in the "doses" employed.

All of the above animals were inoculated subcutaneously with 1.0 cc. of a heavy suspension of H37. These virulent inoculations were made twenty-four hours after the last daily reinfection of the members of lots 1 and 2,—at a time, therefore, when intoxication, if it existed, could be presumed to be still present. In general, the animals of lot 1 had a good, though reduced, tissue allergy, while in those of lot 2 allergy was low. Six weeks later, all guinea pigs were killed, and examined at autopsy.

Results: The guinea pigs of lot 4, originally normal nonimmunes, had the generalized visceral tuberculosis that we are accustomed to find after six weeks' infection with large subcutaneous "doses" of H37.

The immunes of lot 3 showed the involvement expected in guinea pigs

given a single inoculation of R1 several weeks before H37 infection. At the most, there was only an occasional small tubercle or two in the spleen, while usually there was no gross visceral disease whatever.

The animals of lot 1 tolerated the H37 infection the best. There was only the slightest and very occasional involvement of the spleen. One got the impression that, if anything, immunity had been increased by the repeated small inoculations into the skin.

The members of lot 2 displayed variable findings. In two guinea pigs the results were as good as the average for lot 3, that is, the animals with standard immunity. But in most instances there was as much involvement as in the nonimmunes of lot 4, or more. In several the disease was excessive, and as severe as any that we had ever seen.

We cannot attempt to explain why several of these guinea pigs, which had had large daily inoculations of R1, escaped much H37 disease and reacted to the latter almost as well as standard immune animals, while others developed extreme tuberculosis. But positive results in the latter are of great significance. They do prove that an established immunity had given way under the repeated and continued influence of intercurrent tuberculous infections. Therefore, even though the exact factors requisite for the "breaking" of immunity are not clear (they may be connected with circumstances of time and dosage), and remain to be determined, we consider as demonstrated the general principle that too frequently repeated reinfection, at too close intervals, and with enough tubercle bacilli concerned, will lead to a depression of immunity that may become dangerous for the animal. Also, no doubt, contributory to the result will be other factors, such as the place of localization of bacilli, which may conceivably have a marked influence on capacity of absorption of focal materials, further spread of bacilli, resulting symptoms of illness, etc. For instance, we cannot imagine that, if all other circumstances except location would be the same, guinea pigs (or any animal) could tolerate comparable repeated pulmonary reinfections with R1 with as little effect as attend those into and beneath the skin. The allergic reactions, themselves, which caused no marked constitutional disturbance when they occurred in the skin, would bring about acute pneumonia in the lungs, and consequently, very likely, grave disease and intoxication, and much more reduced immunity.

The general result, described above for lot 2, was duplicated and confirmed in a small series of guinea pigs, which were first sensitized and

immunized, then given daily subcutaneous inoculations of living R1 for thirty-seven days, and, twenty-four hours later, a heavy inoculation of H37. In half of these the resulting involvement was fully up to the standard found in the known immune animal, while in the other half it was extreme, and more advanced even than the average in normal controls. There can be no doubt that repeated reinfection at close intervals can "wreck" a specific immunity, although, as stated above, under what precise conditions is obscure.

Summary of Part I

1: Scientific facts proved: (1) That tuberculo-allergy is reduced by repeated reinfections, at close intervals, with tubercle bacilli of low virulence. (2) That, with the inervals between reinfections equal in both instances, allergy is depressed more by large numbers of tubercle bacilli than by small numbers. (3) That, when large enough dosage is reached, chronic intoxication of the animals sets in. (4) That, when large enough dosage is reached, tuberculo-immunity is adversely affected; to an extent that bacilli of virulence may cause more disease than in nonimmune animals. (5) That, if immunity can, in the manner described, be depressed to such an extent as to allow bacilli of low virulence to set up progressive disease, this must happen only after exceptionally large "dosage" of bacilli. Our own attempts to bring about such a condition failed.

2: Inferences supported, but not proved: (1) Reduction of tuberculo-immunity is, in general, dependent upon depression of allergy. (2) It is also conditioned by the presence of intoxication and especially the latter's quantitative relations. (3) The relation of tubercle *within* the body to the body's specific allergy and immunity must be viewed as a continuing interplay between two forces (tubercle and allergy or immunity) operating under endlessly varying conditions of time, mass and place.

Part II: Experiments involving daily reinfections with virulent H37 tubercle bacilli

The experiment to be reported is long and involved, mainly because of the numerous sets of animals necessary to control all variable factors. Its general purposes were similar to those of *Part I:* to reinfect allergic and immune guinea pigs daily, thus simulating, as regards the two prop-

erties of allergy and immunity, our hypothetical focus or foci "feeding" over living tubercle bacilli to the body of the tuberculous subject; and to observe the influence of these frequently repeated infections on established allergy and immunity. The chief interest and importance of the experiment lay in the fact that, instead of R1 bacilli as in *Part I*, living H37 bacilli were always used in daily reinfections. To avoid the unpleasant and perhaps dangerous situation occasioned by numerous animals for weeks and months discharging to the outside large amounts of virulent pus from subcutaneous abscesses, the subcutaneous route for the daily infections was discarded in this experiment, and only intracutaneous inoculations were employed for this purpose.

In inoculating guinea pigs with living virulent tubercle bacilli intracutaneously, we are accustomed to introduce 0.1 cc. of a moderately dilute filtered suspension, averaging 10 to 20 bacilli to the oil-immersion field. The infection that results from such a single inoculation of H37 in a nonimmune is very slow and chronic, and the animal lives, as a rule, for months. No doubt, much of this mildness and chronicity of infection is to be ascribed to the relatively few bacilli concerned. But for a long time we have been gaining the impression (although it lacks definite proof) that, *within certain limits* of quantity, more slowly evolving and less disease will follow the introduction of the same number of bacilli within than beneath the skin.[5] We have thought that perhaps the more compact skin offers more of a barrier to the initial spread of bacilli than does the looser areolar tissue of the *subcutis*. Our ordinary subcutaneous inoculations are performed with from 0.5 to 1.0 cc. of heavy suspensions of bacilli. These infections suffice to bring about generalized visceral tuberculosis in the nonimmune within from four to six weeks after infection, while the earliest changes in the spleen, the internal organ to show tubercle first, are visible from about the twentieth day on.

This experiment began with four different sets of guinea pigs, with 20 to each set. There were, *first*, the sensitized, immunized animals, which were to have daily infections with H37. There were, *next*, those

[5] Differences of normal tissue "resistance" are also to be noted as between the subcutis and peritoneum. For years we have made, whenever possible, all inoculations of specimens for diagnosis subcutaneously rather than intraperitoneally, because we frequently noticed that, when very few bacilli were concerned, subcutaneous inoculation would be followed by tuberculosis while intraperitoneal inoculation would "miss" infection.

immunized animals, which were to receive a single intracutaneous infection with H37; and thus set the standard for what disease *one* H37 inoculation should set up in the immune animal. There were, *third*, those normal guinea pigs, originally nonimmune, which were to be inoculated *daily* with H37; and thus establish the extent of disease that repeated H37 infections should cause in animals lacking the benefit of preliminary immunization. And, *last*, there were those which, normal and nonimmune, were to be given a single H37 infection; and thus disclose the changes brought about by *one* intracutaneous H37 inoculation operating without the opposing force of immunity. By employing four series of animals we expected to establish (1) the normal invasiveness of a single H37 infection,—with the last lot; (2) the degree of our original immunity to such a standard infection,—with the second lot; (3) the effect of repeated infection on this immunity,—with the first lot; and (4) the disease ordinarily set up by such repeated infection in nonimmunes,—with the third lot. This arrangement of control and cross-control may be made clearer by the following summary:

Lot 1: Sensitized and immunized. To have daily intracutaneous infections with H37, that the influence of this frequently repeated reinfection on allergy and immunity might be observed.

Lot 2: Sensitized and immunized. To have a single intracutaneous reinfection with H37, that the grade of conferred allergy and immunity might be established.

Lot 3: Not sensitized nor immunized; normal. To have daily intracutaneous infections with H37, that the results of repeated H37 inoculations in originally nonimmunes might be compared with the results of similar reinfections in the immunes of the first lot.

Lot 4: Not sensitized nor immunized; normal. To have a single H37 intracutaneous infection, that the result, a standard of H37 invasiveness, might be a basis of comparison for the appraisal of all other animals.

Progress of the experiment: The animals of lots 1 and 3, immunized and nonimmunized respectively, were given intracutaneous inoculations of 0.1 cc. of freshly made suspensions of living H37 bacilli *for 70 successive days*. Those of lots 2 and 4, the former, immunes, and the latter, nonimmunes, received a single intracutaneous inoculation (0.1 cc.) of living H37 on the day when the repeated infections of lots 1 and 3 were begun.

The guinea pigs of lot 1 began by reacting well to the first inoculations

with H37. By the end of a week reactions became less vigorous, and perhaps the lowest level of reactivity was reached in the third and fourth weeks. Later, reactions again improved somewhat. Always, a fair capacity to react persisted. During the first three weeks the animals gradually lost ground physically, falling off in weight and in muscular tone and appetite. Throughout this time, while all other animals appeared to be in the best of condition, they were the only ones which seemed to be affected by the inoculations. Afterward, they gradually regained their tone as their reactions improved.

Lot 3, made up of normal nonimmunes which were receiving the same daily infections as lot 1, presented a striking contrast to the latter, especially early in the experiment. During the first few days they showed no effects whatever, as, being nonallergic, they did not react to the earliest inoculations. Toward the end of the first week, as primary nodular tubercle began to appear at the sites of the first inoculations, they began to react allergically; on the fifth day about two-thirds of the animals were giving signs of reactions. By the beginning of the second week sensitization was well established. For two weeks sensitiveness increased, until, by the end of the third week, it had reached a high level. Then some diminution set in, to be followed again by enhancement of allergy (at six weeks). As time went on, these animals gradually became the worst of all in physical condition.

The immunized animals of lot 2, which had been given a single H37 infection, remained in first-class condition throughout, and were at all times the healthiest guinea pigs of the experiment. The nonimmune controls of lot 4, which had been similarly inoculated with H37, began to show local skin tubercle at the end of the first or the beginning of the second week. As the experiment progressed it became more and more probable that the single small infection was setting up a very slow and relatively mild disease; for none of the animals were showing any outward evidence of illness. A sample, taken from this lot and killed on the twenty-eighth day, disclosed that tubercle had not yet got under way in the viscera (spleen, etc.). In another, killed on the thirty-fourth day, there were only a few minute tubercles starting in the spleen. In a third, examined on the fifty-sixth day, there were moderate involvement of the spleen and several small tubercles in the lungs.

As it became evident that disease was progressing with great slowness, we resolved, on the seventieth day, to kill half of all the animals and compare the findings in the several lots, and test the relative immunity

of the survivors with a single "massive" infection of H37. As we noted at the time, and just before the animals were killed and autopsied, "The net result after ten weeks of daily virulent infection is to indicate that daily intracutaneous inoculations of 0.1 cc. of our suspensions of H37 are not great enough to break resistance markedly."

Pathological findings after 70 days of daily reinfections: In lot 4 was to be seen the normal evolution of a single intracutaneous infection with H37 in nonimmune animals after ten weeks. There were marked enlargement of the regional lymph nodes; moderate nodular involvement of the spleen; slight focal infection of the liver in several animals; minimal or no involvement of the lung; and, in general, marked enlargement and induration of the tracheobronchial lymph nodes.

In lot 2, as contrasted with lot 4, could be seen the immunizing effects of preliminary R1 treatment against the same H37 infection as suffered by lot 4. There was no visceral tuberculosis, except for an occasional small nodule in two or three spleens; practically no tracheobronchial adenopathy; and usually no visible regional lymph-node involvement. These animals fared the best.

In lot 3 could be observed the results of 70 successive daily infections in originally nonimmunized animals. The spleens and livers were markedly involved with caseous nodular tubercle; the lungs had slight or moderate tuberculosis; the tracheobronchial lymph nodes were enormous, as were the regional lymph nodes. These animals were uniformly by all odds the worst.

The animals of lot 1 could be contrasted with those of lot 3, to observe whether their preliminary immunization with R1 influenced repeated daily infection with H37, and with those of lot 2, to determine whether such repeated infection modified immunity. The animals were in very good condition. They had not nearly the visceral disease of the controls of lot 4; that is, protected by a single immunizing infection (R1), they withstood 70 daily virulent infections a good deal better than nonimmunes resisted a single virulent inoculation. They were immeasurably better than the members of lot 3. Indeed, they were very little worse than the animals of lot 2, the immunes given a single H37 infection; they had slightly more nodular splenic tubercle than the latter, and more involvement of the regional lymph nodes.

What was especially noticeable in the members of lot 1 was a fine plastic exudate over every spleen and over all the livers but two. This condition was not to be observed in any guinea pig of the other three

lots. It may be compared with the polyorrhomenitis noted as occurring in *Experiment A*, in those animals first immunized and then given large daily infections with R1 subcutaneously.

The leading impression which one derived from the outcome of this experiment was one of tremendously enhanced respect and admiration of the efficiency of tuberculo-immunity as an agent of defense. Even years of first-hand acquaintance with the phenomenon had not prepared us to find it operating to such effect. It was plain that until certain limits of dosage are exceeded, or as long as reinfections do not crowd too frequently or (perhaps more important) too closely upon one another, an immunity due to established infection will take care of a surprising amount of new infection,—certainly, *as long as no disturbing environmental factors are at work.*

In the course of the experiment we had the opportunity to observe the influence of pregnancy and the puerperium on frequently repeated infection. Through an oversight a pregnant animal was included in lot 3, which had daily reinfections without having been first immunized. Since she littered just thirty days after H37 infections had been begun on her, she must have been at about midterm when she received her first infection. She was discovered to be pregnant in the third week of her daily inoculations, when she was isolated in a separate cage and given unusually good individual care. During pregnancy she reacted well and kept in good condition. She bore two young, which lived only six days. After the birth of her litter, she declined rapidly. At once her allergy became greatly depressed, and she began to look quite ill. However, ten days after labor, reactivity was noticed to be increasing again. Meanwhile, there had been no interruption in her daily inoculations. Her improvement was only transitory; she continued to lose weight steadily; at last, she failed to show any allergic reaction to the daily reinfections; and, when killed after her seventieth inoculation, she was in very miserable condition. At autopsy, she was found to have by far the most advanced tuberculosis of all the animals. It may be emphasized that the decisive change for the worse came, not *during* pregnancy in her case, but suddenly and immediately after labor.

Further disposition of survivors: After the seventieth daily inoculation there remained the survivors (one-half) of the four lots, which had not been killed. We had decided to test the immunity of all by giving them a large single inoculation of living H37. Accordingly, every guinea pig received subcutaneously 1.0 cc. of a heavy suspension of

H37. Inasmuch as all animals were tuberculous at the time of this infection, they had to be regarded as immune in varying degrees. It was therefore necessary at this time to add two new series of guinea pigs in order to control the normal infectiousness of this last subcutaneous inoculation of H37, as well as its infectiousness under standard conditions of immunity. The two series were as follows:

Lot 5: Immunized with R1, one and three months previously.
Lot 6: Normal, nonimmunes.

Both lots 5 and 6 were inoculated subcutaneously with 1.0 cc. of H37, of the same suspension and at the same time as lots 1 to 4. For the former two lots it was the first and only infection with H37. Forty-four days later the animals of all six sets were killed and autopsied.

Results: The animals which fared best were those of lot 5, which had received the single test inoculation of H37 after having been immunized. Three had no visceral tubercle whatever, while in the remaining three there was only slight nodular tubercle of the spleen. In striking contrast were the members of lot 6, which had been given the single H37 inoculation without preliminary immunization. With one exception, there was advanced and generalized tuberculosis in all.

Running close to lot 6 were the animals of lot 3. They had just as much tuberculosis, and more, but their condition appeared more chronic, as manifested by the anaemia of the organs and the extensive fatty and sclerotic degeneration of the livers, a common finding in chronic, advanced tuberculosis of guinea pigs. These animals, it will be remembered, were those which had had daily skin infections without previous immunization.

Lot 4 came off surprisingly well. Its guinea pigs had, in no instance, worse than moderate tuberculosis. It was apparent that, although these animals were given their single skin inoculations while they were nonimmune, the small numbers of H37 concerned had set up only a mild and sluggish tuberculosis, which had immunized them satisfactorily against the heavy subcutaneous inoculation. Better than these, but not quite so good as lot 5, were the animals of lot 2, those originally immunized to a single skin inoculation of H37. In 5 of 11 animals there was no visceral tubercle, while in the other six the disease was slight and confined to the spleen (that is, in the viscera).

There were 6 guinea pigs of lot 1. In type and extent of involvement, there was, on the average, very little to choose between them and lot 4;

although, as was noted at the time, lot 4 resulted "perhaps better than lot 1." When the other animals were killed, after having received 70 skin infections, lot 1 appeared to have less tuberculosis than lot 4. It is therefore just possible that the daily skin inoculations, given to lot 1, did lower immunity sufficiently for the animals to acquire a little more disease from the massive subcutaneous infection with H37. (It must not be forgotten that lot 4, originally nonimmune, were immune at the time of the last H37 inoculation.)

COMMENT

It cannot be imagined that the above experiments have settled the question which we ventured to solve. Yet, it would seem that they have contributed some direct scientific support to opinions and impressions derived from experience in the clinic and in the laboratory. It has been shown, under controlled conditions, that, under certain circumstances, frequently repeated specific reinfection does depress both allergy and immunity; and we have been confirmed in our idea that specific intoxication is a potent factor in unfavorably influencing immunity. However, we have been unable to demonstrate the sequence, which, in the paucity of our knowledge, we at present presume to be in operation; that is, reinfection influences allergy and releases intoxicating protein products, and intoxication, in turn, reacts back upon allergy and also influences immunity.

But, one feature of the whole matter, that does stand out prominently in these experiments at every turn, is the prime importance of relations of mass and time in arriving at any given effect. Considered purely by themselves, and without regard to the many influential circumstances of environment and accidents of place, allergy and immunity respond to reinfection in two opposite ways, as factors of quantity and time of reinfection move toward one or the other of two ends of the scale. There is a dosage of reinfection and a spacing of intervals between reinfections, one of which is always to be correlated with the other, which are favorable for the highest development and increase of allergy and immunity. But there is also a dosage and a spacing which will depress and (perhaps) destroy each. The potentially illimitable relations of tuberculous foci to the bodies in which they reside render necessary the presumption that every conceivable effect on allergy and immunity by them is possible. We several times called attention to our purpose to attempt to

reproduce in experiment those conditions of reinfection, which, we may believe, are at work in the body that possesses discharging or metastasizing foci. Our reinfections were graduated to daily intervals. Those from "feeding" foci are surely not spaced so neatly or so regularly. There is no reason to believe that they may not be going on at intervals of minutes, and, on occasion, over a long period of time. And therein may lie a fundamental difference as regards ultimate effects.

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Harry Gilmore Carter

1886-1926

Harry Gilmore Carter died suddenly of haemoptysis on April 10, 1926, at the Piedmont Sanatorium, Burkeville, Virginia. He had been Medical Director of the institution for eight years, having gone there after a six months' association with Lyman at the Gaylord Farm Sanatorium in Connecticut.

Carter was a Virginian through and through. Except for his short residence in New England his entire life was passed in the Old Dominion. He gave much to the State—as he matured, all that a physique and personality touched by tuberculosis could give. No wonder, then, that the State grew to be proud of him and that expressions almost of despair marked the grief that attended his passing. When Virginia in 1918 opened the Piedmont Sanatorium for its consumptive negroes it was taking first steps to grapple with a problem, which is not the least for the South and which is peculiarly the latter's own. More than merely caring for tuberculosis among the more unenlightened of its population, whose position in the household especially favored the spread of infectious disease, a State Sanatorium for negroes envisaged unequalled opportunities for instruction in personal hygiene.

Carter was quick to see and seize these opportunities. From the very beginning, though handicapped by ill health, he conceived sanatorium superintendence as being something more than perfunctory medical direction and institutional stewardship. He used his favored position to begin at once the study of tuberculosis among the negroes. The black race does seem to have its peculiarities in respect to the disease, and Carter set out to study these. From time to time he reported his discoveries in the REVIEW; and just before his death he had completed what must be his last contribution, which will appear in these columns later. Letters that have come to the writer are impressive, as testifying to the high regard in which the man and his work were held throughout the Southern States. All express sentiments of having suffered a loss that will take long to assuage and replace.

Harry Gilmore Carter was born in Lancaster County, Virginia, November 8, 1886. He received his education in a private school at Kilmarnock and in William and Mary College, from which he was graduated, A.B., in 1908. After two years as principal of the High School at Heathsville, he entered the Medical College of Virginia, receiving there the degree of M.D. in 1910. Then followed an interneship of one year at the George Ben Johnston Memorial Hospital at Abingdon, after which he began private practice in Emporia. Eighteen months later he broke down with pulmonary tuberculosis, and went to the Catawba Sanatorium of Virginia. On November 1, 1917, he entered upon his work as Second Assistant Physician at Gaylord Farm Sanatorium, from where he went to the Piedmont on April 1, 1918. He was a member of the National Tuberculosis Association, Southern Medical Association, and the American Medical Association. He received recognition for his medical contributions by election to Phi Beta Kappa. These contributions number about ten papers, of which the more important, on tuberculosis among the negroes, have been published in the REVIEW.

He was married on June 28, 1916, to Miss Mabel Holland, of Baltimore, Maryland, who, with two children, a daughter and a son, survive him.

A. K. K.

Corrections

In the paper by Westergren, *The Technique of the Red Cell Sedimentation Reaction*, July, pp. 94-101, the following corrections should be made:

Page 96, line 3: For *1 cc.* read *0.1 cc.*

Page 99, line 11 from bottom: For (*or 1.5 to 0.5 cc. ....*) read (*or 1.5 or 5 cc. ....*).

THE CONTAGION OF TUBERCULOSIS[1]

EUGENE L. OPIE AND F. MAURICE McPHEDRAN

The contagion of phthisis has been the subject of controversy ever since the beginning of recorded medical history. Some have maintained that the disease spreads like an epidemic, whereas others have found no evidence that the diseased can infect the healthy. The factors concerned are so complex that evidence may be found to support any shade of belief.

The opinion that every individual in congested centres of population is infected with tuberculosis is widely accepted; but, although tuberculosis is one of the most accessible examples of endemic disease, knowledge concerning the spread of this nearly universal latent infection is vague, and its relation to manifest disease is almost wholly unknown.

Infants and young children exposed to tubercle bacilli, discharged by adults with phthisis, often acquire fatal tuberculosis; but opinion concerning the transfer of infection from one adult to another varies widely, and many of those who have considered this subject maintain that all phthisis of adults is acquired in infancy or in later childhood.

Latent tuberculosis may be defined for convenience as that which is unaccompanied by symptoms or physical signs, causes no obvious disturbance, and is not recognized by the physician. There is no sharp distinction between latent and manifest tuberculosis, and in some instances latent tuberculosis is more extensive than that which is recognizable. Ability to distinguish between latent and manifest disease will vary with the means available for diagnosis. Quantitative intracutaneous tuberculin tests and roentgenological methods, especially adapted to the purpose in view, have been used for the identification of latent lesions.

The present investigation of latent tuberculosis in children has followed a study of the pathology of latent tuberculosis made by one of us during the last ten years (1). This study has shown that the separation of an infantile and an adult type of latent pulmonary tuberculosis is essential to an understanding of the disease. The infantile type, occurring in a child previously uninfected, begins as a focus in any part of the lung, and

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia.

is associated with caseous lesions of those pulmonary lymph nodes which are nearest in the direction of lymph flow. In the first year of life tuberculous infection is usually but not always progressive and fatal, and exhibits the characters of experimental tuberculosis in a susceptible animal; but with increasing age the tendency to heal increases, so that at the age of eighteen almost every individual possesses caseous encapsulated and more or less completely calcified focal lesions of the lungs and tracheobronchial lymph nodes.

The adult type of pulmonary tuberculosis begins in the apex of the lung and is unaccompanied by tuberculous lesions of adjacent lymph nodes. It occurs in lungs in which focal lesions of lungs and lymph nodes are found (2), and has the characters of a second infection. There is no evidence to support the view that the apical lesion of the adult is derived from the focal lesion of childhood, for these lesions are often completely healed and calcified when the apical lesion is caseous, and in at least half of the lungs in which each type is limited to one lung one lesion is in one lung and the other on the opposite side. It is noteworthy in this connection that the incidence of latent apical lesions increases with age, being in a series of autopsies studied several years ago 8.7 per cent between the ages of 18 and 50 years and 28.6 per cent in later life.

There is every transition between the latent apical lesions of those who die with diseases other than tuberculosis and the fatal phthisis of adults. Latent apical tuberculosis has been found in one of five (3) of all adults who have died from causes other than tuberculosis, the incidence increasing with age.

The infantile or focal type of pulmonary tuberculosis is almost invariably found during the first decade of life, but in children which have once been infected the adult type may make its appearance. In the second decade of childhood fatal pulmonary tuberculosis in some instances has the character of the infantile type, and in other instances conforms with the adult type.

A few individuals escape infection during childhood and in adult life suffer with the infantile type of the disease. In this country (4), the negro escapes infection during childhood more frequently than the white and, in consequence, pulmonary tuberculosis resembling the infantile type, with primary localization in any part of the lung and massive caseation of adjacent lymph nodes, is more frequently found in the adult negro than in the adult white, and is at times accompanied by general miliary tuberculosis.

In the consideration of latent tuberculosis in children it is desirable to bear in mind the occurrence of infection by way of the gastrointestinal tract. It is not improbable that a positive tuberculin reaction in a few instances is referable to lesions of the intestine and mesenteric lymph nodes produced by milk containing bovine tubercle bacilli. The incidence of obsolete tuberculous lesions of the mesenteric lymph nodes in this country is probably not more than 5 per cent, whereas in Great Britain, where bovine tuberculosis is more common, this form of infection is far more common (5).

STUDY OF FAMILIES

The use of charts which depict an entire household has been an essential aid in correlating data concerning tuberculous infection (see fig. 3, etc.).

Vertical lines represent each member of the family, and correspond in length with the duration of residence within the household. They are erected upon a horizontal line representing the date at which the family came under observation, and in most instances show the duration of married life of parents and the ages of children. Whenever a member of a family leaves the household the corresponding line is broken, for example, by residence in a sanatorium. Observations made after the original date of the chart are recorded below the horizontal line representing this date.

Symbols are used to indicate the most important data concerning the progress of tuberculous infection. A heavy black column at the right of the life-line shows that the individual has suffered with manifest tuberculosis during the period which is indicated. A second heavy black column on the left of the life line indicates that during the corresponding period tubercle bacilli have been present in the sputum. If a horizontal band is projected across the chart corresponding to tuberculosis in any member of the household, it will measure the period during which all other members have been in contact with the disease.

Signs, which will be defined later, indicate the absence or presence and severity of the tuberculin reaction. A heavy cross upon the life-line shows that roentgenological examination of the chest has been made with negative result. A heavy black dot indicates that a focal tuberculous lesion has been found within the lungs, and an encircled dot represents tracheobronchial tuberculosis. An arc across the line, with a salient

from it pointing downward, is used to show that a latent apical lesion has been found.

The chart serves as a guide for the medical and nursing care of the family. It shows how much manifest and latent tuberculosis exists in the family. It suggests means by which further spread of infection may be prevented, and emphasizes the desirability of procedures directed to prevent the transition from latent to manifest disease. These charts furnish abundant evidence that the control of tuberculosis should be undertaken with the whole family in view.

In the year 1923–1924 (September to September) 102 families came under observation, and during the subsequent three years the progress of tuberculous infection in these families has been followed. The present report is limited to this group, but our conclusions have been confirmed by the larger number of families seen later. In 1924–1925 approximately 250 additional families have been included in the study, and during the present year the staff of the Institute has adopted a system of records, by means of which all individuals who apply to the dispensary will be included with the scope of this investigation. We have had the helpful coöperation of Dr. H. R. M. Landis, Director of the Clinical and Sociological Departments of the Henry Phipps Institute. We have received valuable assistance from Dr. Joseph Aronson (6), who has supervised the tuberculin tests. Dr. R. K. Childerhose has assisted in clinical and roentgenological work. Families have been visited at frequent intervals by social workers under the direction of Miss Fannie Eshleman. Throughout the investigation Miss Anne Steeves has assisted in the roentgenological laboratory, and Miss DuFour has collaborated in the collection of data concerning patients. To these and to many others we are indebted for earnest and able assistance.

During the years 1923–1924 and 1924–1925 the study was aided by generous appropriations from the National Tuberculosis Association assigned by its Medical Research Committee.

The intracutaneous tuberculin reaction has been used, and Old Tuberculin, in quantities varying from 0.00001 to 0.001 cc., has been injected. The strength of tuberculin has been determined by intracutaneous tests on guinea pigs, and only very active tuberculin has been employed. The quantity of the sample tested has been large enough to permit its use during several months, and within this period only one sample has been used. The first test has been made with 0.00001 cc., or 0.01 mgm., of Old Tuberculin, diluted to 0.1 cc. and injected into the cutis. The site

of injection is examined two days later, and if no reaction has occurred a second injection of 0.0001 cc. (0.1 mgm.) in the same volume as before is made. If there is no reaction again after two days, a third injection with 0.001 cc. (1 mgm.) of tuberculin follows. It has not seemed desirable to use the larger quantities recommended by Happ and Casparis (7). The intensity of the reaction has been recorded as one plus (+) when redness has been present in an area from 10 to 15 mm. in diameter. Inconspicuous spots of redness, or redness with no oedema, have not been regarded as definite evidence of hypersensitiveness to tuberculin. Reactions with redness and oedema in an area from 15 to 25 mm. in diameter have been designated two plus (++). Extensive redness and oedema measuring more than 25 mm. have been recorded as three plus (+++) or, if accompanied by necrosis of the skin, as four plus (++++).

By means of roentgenological examination it is possible to identify in the lungs of children and adults the various lesions of latent tuberculosis which are recognizable in the lungs at autopsy. Automatic synchronization of roentgen-ray exposures, introduced by one of us (8) in collaboration with Mr. Charles N. Weyl, has been used, and has signally aided the interpretation of plates. The identification of lesions has been assisted by a parallel study of similar lesions depicted in roentgenograms of lungs removed postmortem and subsequently examined directly.

Stereoscopic plates soon showed that the lungs of almost every child and adult contain sharply defined spots which suggest the presence of calcified nodules. Study of these nodular spots, and comparison with lesions seen in roentgenograms prepared from excised lungs, showed that most of them do not represent focal lesions of the lung, but are caused by vascular trunks directed toward the plate. An evenly circular spot, from 3 to 6 mm. in diameter, is almost invariably found in one stereoscopic plate near the hilum of the left lung at the level of the fifth interspace posteriorly, and a similar spot is almost as frequently seen on the right side at the same level, but they are often absent in the other stereoscopic plate. Smaller circular shadows are frequent throughout the median half of each lung field below the level of the fourth rib posteriorly. A vascular trunk may often be traced to these circular spots, and there can be no doubt that they are caused by vascular trunks directed in the axis of the ray. They disappear when the relation of the patient to the plate is changed. Calcified nodules are recognized by their duplication in stereoscopic plates, by their persistence in oblique anteroposterior or obliquely lateral plates, by their sharp and often irregular

outline, and in many instances by their position in the periphery of the lung field (the median half of the base excepted). These calcified nodules are usually from 2 to 6 mm. across, but may be larger. It is probable that small caseous lesions cast inconspicuous shadows and are often unrecognizable; but roentgenograms prepared from lungs excised after death show that the calcium content of caseous nodules may vary widely, for caseous nodules may cast an opaque shadow even though the putty-like centre of the nodule contains no hard particles and does not grate when cut. Nevertheless it is evident that roentgenological examination fails to disclose many early tuberculous foci within the lungs and, furthermore, it is probable that calcified nodules are not infrequently hidden by opaque structures overlying them.

Lesions of the tracheobronchial lymph nodes have assumed outstanding significance in the recognition of advanced latent tuberculosis, and serve as an index to possible development of manifest disease. Enlargement of the mediastinal shadow and accentuation of the shadow at the hilum of the lung have been of no assistance in the recognition of disease of pulmonary lymph nodes. The lesions which will be described have been demonstrable as well-defined masses, in contact with the trachea near the bifurcation or beside the main bronchial stems. Comparison with lesions seen after death indicates that opacity of the affected tissue is referable to deposition of calcium salts within caseous material, but furnishes no proof that the lesion has healed. Masses from 1 to 3 cm. across are found near the hilum of one or other lung, or within the mediastinum. Films made with the patient in an obliquely lateral position often show that tuberculous lymph nodes within the mediastinum are situated at the bifurcation of the trachea, in greater part below one or the other bronchus, or beside the trachea above the bifurcation, and with few exceptions on the right side. It is often evident that an oval mass in one of the positions named is made up of small opaque particles, which are closely grouped together and give the whole a coarsely granular appearance. The lesion found at autopsy often exhibits this character.

Latent apical lesions, seen in roentgenograms made from the chest, reproduce the characters of lesions found in the apices of the lungs of adults who die from causes other than tuberculosis. In some instances a cap of fibrocaseous tissue, with strands extending downward into the lung substance, occupies the summit of the apex, and tends to progress beneath the adjacent lateral aspect of the lung. In the chest plate an opaque

shadow is seen beneath the border of the second rib, and from it pointed projections or salients extend downward. In other instances the apical lesion occurs as a well-defined, often somewhat rounded, fibrocaseous mass within the substance of the apex, usually below the external aspect and one or two centimetres from the summit. In stereoscopic films lesions of this character are represented by well-defined rounded shadows, which extend from below the second rib into the second interspace and perhaps downward into the third or even into the fourth interspace. Shadows of several separate masses may be seen, and their position is more often lateral than median. The latent lesion being defined as one not associated with recognized symptoms or physical signs, the character of the apical lesion has varied widely. In some instances the ring of the first rib has been filled with a flocculent cloud, whereas in a few instances fairly advanced tuberculous lesions have occupied the upper parts of both lungs.

CONTACT WITH TUBERCULOSIS IN FAMILIES

Families in which some member suffers with pulmonary tuberculosis have been compared with those which are free from manifest disease. It will be convenient to separate families in which a parent is tuberculous from those in which one of the children suffers with the disease, and in each instance a further division may be made in accord with the presence or absence of tubercle bacilli in the sputum of the affected individual. There is a small group of families in which tuberculosis has been suspected but not confirmed (possible contact). It has seemed desirable to consider infection of children and of adults separately.

Fishberg (9) studied the frequency of the tuberculin reaction tested by Pirquet's method in children exposed to contact with tuberculosis, and found that it was present in 67 per cent of the children which were tested. In children exposed to tuberculosis Schram (10), Slater (11) and others found the Pirquet reaction more frequent than in other children. Only slight difference was found by Austrian (12) between children exposed to contact with fatal tuberculosis or with those known to have tubercle bacilli in the sputum (77.7 per cent) and those with no known exposure (68.8 per cent). Among 1,234 children whose parents had had tuberculosis Drolet (13) found that the Pirquet reaction was present in 64 per cent, whereas among 461 children whose parents had had no tuberculosis the reaction was present in 66 per cent.

Thirty-three families, in which there has been no history of contact

with tuberculosis, furnish a basis for comparison with families in which some member has suffered with the disease (fig. 1). The group is not

FAMILIES WITH TUBERCULOSIS IN PARENT (TUB. BAC. IN SPUTUM)								FAMILIES WITH NO HISTORY OF TUBERCULOSIS							
FAMILY	FATHER	MOTHER	NO LESION	PULMONARY NODULE	TUBERCULOSIS TRACHEO-BRONCH. NODES	LATENT APICAL	MANIFEST TUBERCULOSIS	FAMILY	FATHER	MOTHER	NO LESION	PULMONARY NODULE	TUBERCULOSIS TRACHEO-BRONCH. NODES	LATENT APICAL	MANIFEST TUBERCULOSIS
Ac	TBC	TBC			◉◉		TBC	Ab			xxx				
Bc	TBC		xxxxxx	●●●	◉			Ba			x				
Ca		TBC			◉◉◉◉			Bd			xxxxx				
Ce	TBC		xxx					Be			x				
Cg	TBC	TBC	x					Bf			xx				
Ck	TBC			●●	◉◉			Bh			xxxxxx	●			
Da		TBC	x		◉		TBC	Bi			xxxx				
Df	TBC		x	●				Ci			x				
Dh	TBC		xx		◉			De			xx				
Do		TBC		●●				Dg			xxx	●●			
Ea	TBC		x	●●●●			TBC	Di			xxxx				
Fe	TBC		xxxxx					Dl			xxx	●			
Ia	TBC		x		◉		TBC	Dm				●			
Ja	TBC		xxxx	●●				Dn			x	●	◉		
Je		TBC	xxx	●●				Fa			xxxxx				
Jf		TBC			◉		TBC	Fb			x				
Ka	TBC			●	◉◉		TBC TBC	Fc			xx				
Mb	TBC	TBC	xx					Fg			xxx	●			
Me	TBC		xx	●●●	◉			Ga			x	●			
Mg	TBC				◉◉			Gc			x	●			
Mh	TBC	TBC		●●●	◉◉◉		TBC TBC	Gd			x				
Ml	TBC		xx	●				La				●			
Na	TBC		xx					Mf			x	●	◉		
Oa	TBC		xxx	●●●				Mi			xxx		◉		
Pb	TBC		xxxxxx	●				Mn			xxx				
Sc	TBC		x	●●●	◉			Oc			x				
Sd	TBC		x		◉		TBC	Pa			xxx				
Sf		TBC	x		◉			Sa			xxxx				
Sk		TBC	x	●	◉			Se			xx	●			
Sm		TBC	xxx	●				Sg			x				
Tb	TBC		x	●				Sh			xx				
Vc	TBC		xxxx	●●				Tc				●			
Ya	TBC		xx		◉		TBC	Va			xxxx	●	◉		
Zc	TBC			●●	◉◉										

FIG. 1. TUBERCULOUS LESIONS FOUND BY ROENTGENOLOGICAL EXAMINATION

(1) In families of which one parent had pulmonary tuberculosis with tubercle bacilli in sputum, and (2) in families of which no member had tuberculosis.

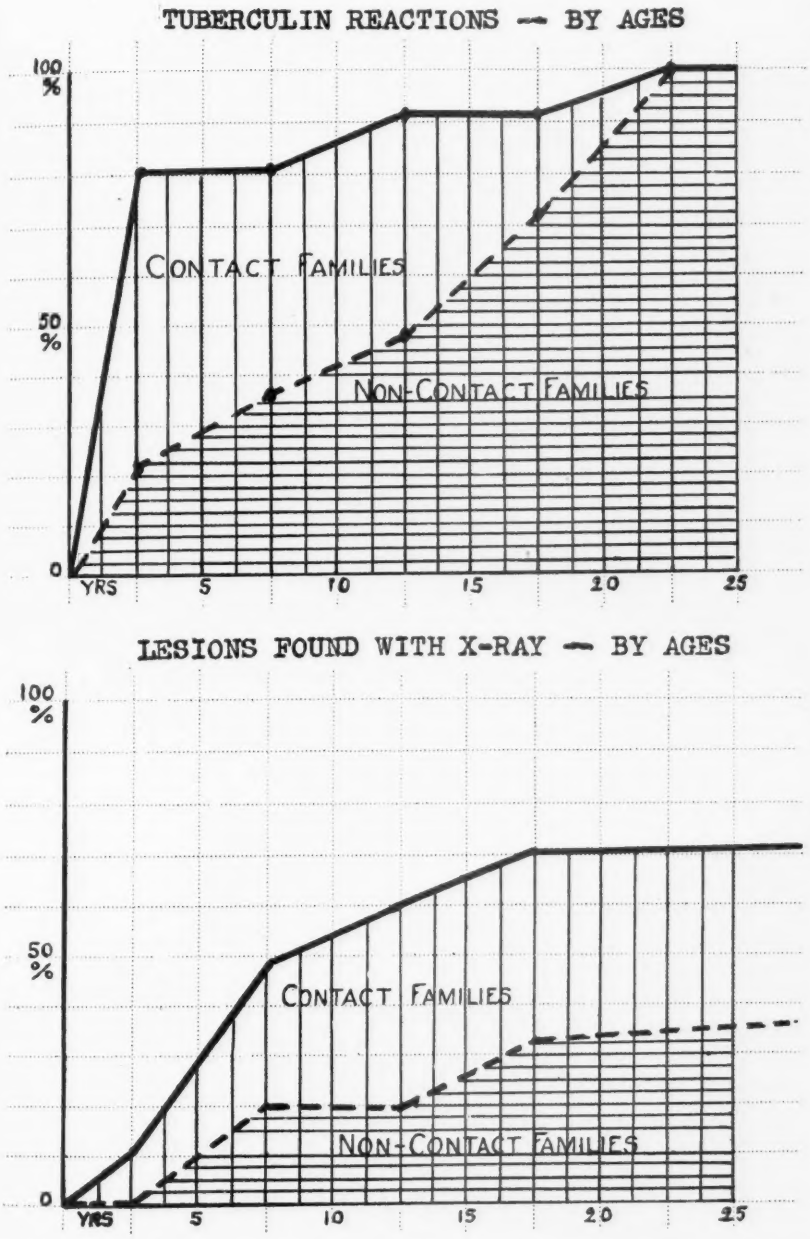

FIG. 2. Charts showing (1) tuberculin reactions arranged by ages in contact and non-contact families and (2) lesions found by roentgenological examination arranged by ages in contact and noncontact families.

a sample of the general population, for excluded from it are all families in which tuberculosis has become manifest in children or in parents. In this group occur families (for instance, families, *Bi*, *Gd* (fig. 3)) in which none of the children react with tuberculin, and roentgenological examination shows no lesions which are recognizable as tuberculous in origin. More frequent are families (for instance, families, *Mi* (fig. 5), *Sa* (fig. 4)) in which younger children exhibit no evidence of tuberculous infection when tested by the tuberculin reaction or examined by roentgenogram, whereas one or several older children aged ten years or more exhibit tuberculin reactions or calcified pulmonary nodules. Nevertheless, although the younger children tend to escape infection, exceptions are not uncommon and in some families with no history of tuberculosis several members have been infected (for instance, families *Fa* (fig. 6), *Mf* (figs. 7, 8)).

It is shown in table 3 and figure 2 that the frequency of positive tuberculin reactions in children of families with no tuberculosis increases gradually from infancy to adult life. Table 4 and figure 2 show that the incidence of latent tuberculous lesions of the lung recognizable by roentgenological examination is less in each age-group than that of positive tuberculin reactions, but gradually increases from zero in the age period from birth up to five years to 33 per cent in the period from 15 up to 20 years of age. Gradual increase of these manifestations of tuberculous infection with age indicates that children of families with no manifest tuberculosis come into contact with sources of infection outside of the family. Furthermore, the occurrence of evident tuberculous infection in younger members of so called "noncontact" families suggests that, with limited opportunities for examination of members of households and their associates, contact with tuberculosis often remains undiscovered.

In 34 families (fig. 1) one parent has suffered with pulmonary tuberculosis, and is known to have discharged tubercle bacilli with the sputum. In three of these families the other parent has had phthisis in two instances with tubercle bacilli in the sputum (families *Cg*, *Mb*), and in one with no tubercle bacilli demonstrable (family *Mh* (figs. 23, 24, 25)). In several families another adult member of the household of the same generation as the parents, usually an uncle or aunt, has suffered with open tuberculosis (families *Ac* (figs. 9, 10), *Ca* (figs. 13, 14), *Jf*, *Ka* (figs. 17, 18), *Sc* (figs. 29, 30)). The duration of contact with open tuberculosis in the whole group has varied from 6 months to 9 or more years, the average length of contact being 4 years and 8

months. It is evident that the children of these families have been exposed to grave danger of infection.

In families with no tuberculosis a large part of the children do not react with tuberculin, and a considerable number react only with large injections of tuberculin (0.1 and 1 mgm.). The relatively small number, which are highly sensitive to tuberculin, reacting with 0.01 mgm., are, as will be shown, older children. In families with open tuberculosis, on the contrary, few children fail to react, reactions of moderate severity are less numerous than in the former group, and reactions of approximately maximum severity predominate.

In figure 1 the frequency of lesions of tuberculosis, demonstrable by roentgenological examination in the two groups of families, have been compared. The difficulties of demonstrating latent tuberculous lesions are considerable, and doubtless many lesions are not found. The high incidence of latent apical tuberculosis in the consorts of parents with open tuberculosis is noteworthy. Latent lesions are much more numerous in children of families with open tuberculosis than in those with no history of the disease. Nodules of focal pulmonary tuberculosis are numerous in the one group and relatively infrequent in the other, whereas the severer types of latent infection, represented by tuberculosis of tracheobronchial lymph nodes and in most instances with recognizable pulmonary nodules, are seven times as numerous in contact as in noncontact families. In two instances latent apical tuberculosis has been found in adolescent children of the contact group. The table shows that several children in certain families with parental tuberculosis have no demonstrable lesions of the disease. It will be shown that contact with the open tuberculosis in these families has been in most instances of short duration.

In 7 families the parents had no manifest tuberculosis, but one of the children suffered with open tuberculosis. In this group the incidence of nodular lesions of the lungs and recognizable disease of the tracheobronchial lymph nodes is high, being together 44 per cent. This figure includes all children who have been examined by roentgen-ray, but in only one instance (*Celia Cm*) has it been possible to obtain roentgenograms of the son or daughter with open tuberculosis. With this exception, figures for children of the group are comparable with those in which a parent with open tuberculosis has been the source of infection, for in one group they represent the effect of contact with an infected parent upon the children of the family and in the other group the influence of disease in brother or sister upon other children of the household.

In this group of 7 families the eldest child has suffered with open tuberculosis in six instances. The age at which tuberculosis was first evident has varied from 14 to 22 years, four children being from 14 to 16 years old, and the average age being 17 years. These figures indicate that the disease has been acquired by contact with tuberculous individuals outside of the family, but no definite information concerning the source of infection has been obtainable.

There have been 13 families in which a parent has had tuberculosis with no tubercle bacilli in the sputum. In these families parental tuberculosis has been established by symptoms, physical signs and roentgenological examination. The frequency of roentgenological evidence of latent tuberculosis in the children is less than that in families with open tuberculosis and greater than that of noncontact families. Since in some families of this group (families *Cl* (figs. 31, 32), *Db* (figs. 21, 22), *Wa* (figs. 33, 34)) all members have either positive tuberculin reactions or demonstrable latent lesions, and in most instances both, it seems probable that the tuberculous parent has recently discharged tubercle bacilli, even though none have been found when examinations have been made. In other families (families *Mc*, *Ra*) the presence of demonstrable latent lesions with negative tuberculin reaction suggests that after dissemination of tubercle bacilli there has been an interval of one or more years, sufficient to permit disappearance of the reaction. In a third group of families (families *Cf*, *Jb*, *Ta*) evidence of latent tuberculous infection is scant, especially in younger children, and as these families resemble those in which there has been no contact with tuberculosis it is probable that the tuberculous parent has discharged few if any tubercle bacilli.

It is noteworthy that in this small group of families latent apical tuberculosis has been found in the consort of the tuberculous parent twice. In two of the older children of families of the group (*Sarah Wa* (figs. 33, 34) and *Jennie Wb* (fig. 35), both aged 15 years) latent apical lesions have been demonstrable.

Three families, in which a child has had pulmonary tuberculosis with no tubercle bacilli in the sputum, require little comment, for in this as in the foregoing group the possibility of occasional discharge of tubercle bacilli must be taken into consideration. In family *Dc*, in which all members exhibit evidence of latent tuberculosis, either by tuberculin reaction or by roentgenological examination, a latent apical lesion has been found in the mother, and suggests with little possibility of substantiation that it may have been a source of infection.

In a group of 11 families with possible contact with tuberculosis one or more members have had symptoms or physical signs which have suggested pulmonary tuberculosis though this diagnosis has not been established, or (in family *Bk*, with mother tuberculous, and in family *Wd*, maternal aunt tuberculous) a known tuberculous relative has had little if any contact with other members of the family. In this group the frequency of tuberculin reactions and of latent tuberculous lesions found by roentgenological examination does not exceed that in noncontact families. In family *Fd* a child (*Joseph*), in whom pulmonary tuberculosis is suggested by physical signs and by diffuse shadows in roentgenograms, has had no tuberculin reaction. The absence of reaction in a brother and a sister furnishes presumptive evidence that the disease is not tuberculous, but the diagnosis remains uncertain. In another family (family *Sb* (fig. 36), with seven children, each with no reaction to tuberculin on first examination), there is so little evidence of latent tuberculous infection that contact with tuberculosis within the family is improbable. Observations made upon families which have come under observation during 1925 support the conclusion that absence of latent tuberculosis in the children indicates that the family has not been in contact with open tuberculosis. Nevertheless, for the present purpose it is obviously undesirable to exclude the diagnosis of tuberculosis upon this evidence.

The incidence of the tuberculin reaction in children of the groups of families just cited has been as shown in table 1.

TABLE 1

The relation of the tuberculin reaction of children to contact with tuberculosis in families

CONTACT WITH TUBERCULOSIS	TUBERCULIN REACTIONS	NUMBER OF CHILDREN EXAMINED
	per cent	
Parent (tubercle bacilli in sputum)	86.2	124
Child (tubercle bacilli in sputum)	64.8	17
Parent or child (no tubercle bacilli in sputum)	41.0	61
Possible contact	50.0	30
No contact	44.5	89

Accurate analysis of these figures can be made only when children are grouped in accordance with age. Nevertheless, it is evident that contact with open tuberculosis within the family is an important factor in the production of latent infection. Tuberculosis in the parent is more infectious than tuberculosis in a brother or sister, but the difference, it will be shown later, is dependent upon the duration of contact.

It is noteworthy that the tuberculin reaction is slightly less frequent in children of households in which there has been tuberculosis with no tubercle bacilli found in the sputum than in families with no evidence of tuberculosis. Nevertheless, table 2 shows that the children of the first group have more latent tuberculosis recognizable by roentgenograms than the latter, and it is not improbable that the tuberculin reaction at one time present has in some instances disappeared later.

TABLE 2

Influence of family contact with tuberculosis upon the occurrence of lesions recognizable by roentgenograms in children

CONTACT WITH TUBERCULOSIS	ALL LESIONS	NODULES OF LUNG	TUBERCULOSIS OF TRACHEO-BRONCHIAL LYMPH NODES	LATENT APICAL TUBERCULOSIS	MANIFEST TUBERCULOSIS	NUMBER OF CHILDREN EXAMINED
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	
Parent (tubercle bacilli in sputum)	53.3	29.8	22.7	0.8(1.6)	(8.9)	124
Child (tubercle bacilli in sputum)	43.5	17.4	21.7		4.4(4.4)	23
Parent or child (no tubercle bacilli in sputum)	29.8	22.8	5.3	1.7		57
Possible contact	22.6	22.6				31
No contact	21.3	16.8	4.5			89

Note: Figures in brackets represent those instances of latent apical or manifest tuberculosis which have been associated with lesions listed in another column.

Table 2 shows the occurrence of tuberculous lesions recognizable by roentgenological examination in various groups of families.

Comparison of tables 1 and 2 shows that tuberculous lesions are not found in all instances in which a tuberculin reaction occurs. The discrepancy has been explained elsewhere. It is noteworthy that in families with open tuberculosis in parent or child approximately two-thirds of the children who react with tuberculin have recognizable lesions, whereas in families with no contact or with possible contact only one-half of those who react have lesions demonstrable by roentgenological examination. Examination of roentgenograms confirms the suggestion that the lesions present in children of contact families are larger and more conspicuous than those acquired outside of the family.

The frequency of tuberculous lesions recognized by roentgenograms is greatest after exposure to contact with open tuberculosis of a parent,

less with that of a sister or brother, and considerably less with tuberculosis when no tubercle bacilli are demonstrable in the sputum. The incidence of tuberculosis of tracheobronchial lymph nodes is high after contact with open tuberculosis in parent or child, but in families in which there is tuberculosis with no tubercle bacilli demonstrable in the sputum this type of disease is scarcely more frequent than in families with no contact with tuberculosis.

THE RELATION OF TUBERCULOUS INFECTION TO AGE

Figures showing the frequency of the tuberculin reaction in any group of children have little value unless they are arranged in relation to age, for almost all adults react to tuberculin and there is a gradual increase in the percentage of positive reaction from zero at birth to approximately 100 per cent at the age of 20 years. The figures in table 3 show the percentage of positive reactions among 451 tests arranged in groups by age.

TABLE 3

Tuberculin reaction in relation to age and contact with tuberculosis

YEARS	CHILDREN OF FAMILIES IN CONTACT WITH TUBERCULOSIS (TUBERCLE BACILLI IN SPUTUM)		CHILDREN OF FAMILIES WITH NO KNOWN CONTACT WITH TUBERCULOSIS	
	Positive	Number examined	Positive	Number examined
	per cent		*per cent*	
0–5	80	15	23.3	9
5–10	80.4	92	35.5	45
10–15	91.1	101	46.2	67
15–20	90.5	21	62	29
20+	100	43	100	29

The effect of contact with manifest tuberculosis upon the occurrence of the tuberculin reaction is here evident (see also fig. 2), for in contact families among children up to the age of ten years approximately 80 per cent react, whereas in noncontact families only from 23.3 to 35.5 per cent give positive reactions.

Even though the tuberculin reaction is an index of the presence of a tuberculous lesion in some part of the body it will not be possible to find lesions of the lungs by roentgenological examination in all individuals with a tuberculin reaction. Early lesions in which calcification has not begun may cast no recognizable shadow, and in the presence of calcifica-

tion overlying opaque tissue may prevent their recognition. Furthermore, tuberculous lesions of the intestines or mesentery occasionally occur, and may render the individual sensitive to tuberculin. Finally, it is noteworthy that the tuberculin reaction may disappear after recovery from tuberculosis both in man and in lower animals.

The grouping of children by age shows that roentgenological evidence of infection lags behind that furnished by the tuberculin reaction, but in each age group in contact families latent lesions recognized in roentgenograms are far in excess of those in noncontact families.

TABLE 4

Latent tuberculous lesions recognized by roentgenological examination in relation to age and contact with tuberculosis

YEARS	CHILDREN OF FAMILIES IN CONTACT WITH TUBERCULOSIS (TUBERCLE BACILLI IN SPUTUM)		CHILDREN OF FAMILIES WITH NO KNOWN CONTACT WITH TUBERCULOSIS	
	With latent lesions	Number examined	With latent lesions	Number examined
	per cent		*per cent*	
0–5	11.1	7	0	8
5–10	47.5	80	20.5	44
10–15	59.8	87	19.5	41
15–20	70.6	17	33.3	9
20+	70	30	35.7	14

Table 4 and figure 2 show the progressive increase of latent tuberculous lesions in families with open tuberculosis, from 11.1 per cent in children during the period from birth up to 5 years, to 70.6 per cent in children from 15 to 20 years old, whereas the corresponding figures in noncontact families range from zero to 33.3 per cent.

THE RELATION OF INFECTION TO DURATION OF CONTACT WITH OPEN TUBERCULOSIS

Charts of certain families with open tuberculosis (families *Ac, Ca, Ck, Do, Ka, Mg, Mh, Zc* (fig. 1, etc.)) show that every child exhibits roentgenological evidence of tuberculosis and in these children advanced lesions have been found. In other families (families *Cf, Fe, Pb, Vc* (fig. 1)) there is, on the contrary, scant evidence of infection. In the first-named class of families there has been contact with open tuberculosis during many years, whereas in the latter contact has been short. Table 5 shows the duration of contact with open tuberculosis of the parent and evidence of tubercu-

lous infection in the children, as measured by the tuberculin reaction and roentgenological demonstration of latent tuberculous lesions.

TABLE 5

Duration of contact with open tuberculosis and evidence of tuberculous infection

DURATION OF CONTACT	TUBERCULIN REACTION		LESIONS FOUND BY ROENTGENOLOGICAL EXAMINATION			
	Number of children	Positive	Number of children	Nodules in lung	Tuberculosis of tracheo-bronchial lymph nodes	With lesions
years		*per cent*				*per cent*
0–1	17	64.7	17	2		11.8
1–2	5	80.0	5	1		20.0
2–3	6	83.3	4	2		50.0
3–4	10	80.0	9	5	1	66.6
4–5	36	97.2	35	11	12	65.7
5–9	25	84	22	9	4	59.1
9 and over	20	95	19	10	2	63.2

Although the number of children in each group is so small that the percentages are only approximately correct, table 5 indicates that nearly maximum frequency of the tuberculin reaction is reached only after one year, whereas maximum incidence of lesions demonstrable by roentgenological examination is not reached until three years of contact with open tuberculosis. Furthermore, it is evident that tracheobronchial tuberculosis first appears after 3 years of contact and is infrequent until 4 years have elapsed. These figures show that contact with open tuberculosis during a period of less than one year fails to sensitize to tuberculin all of those who are exposed. After one year focal lesions produced by contact with open tuberculosis have undergone those changes which make them visible in roentgenograms and after 3 years have reached maximum frequency. Recognizable lesions of tracheobronchial lymph nodes, which are most numerous after the lapse of one more year, are the result of exposure to tubercle bacilli in great number during a long period.

The occurrence of latent apical tuberculosis in this group of families will be discussed later.

THE RELATION OF THE TUBERCULIN REACTION TO RECOGNIZABLE LATENT LESIONS

The tuberculin test is readily applied to many children, whereas roentgenograms are obtained with much greater difficulty. It is desirable

to know whether the tuberculin reaction can be used as an index of the presence of lesions recognizable by roentgenograms, and especially whether there is a close correlation between the severity of the tuberculin reaction and the extent of recognizable tuberculous infection. In children less than 5 years of age latent tuberculous lesions have seldom passed into the stage in which they are recognizable by roentgenograms and are much less frequently identified than in older children, being present in only one out of 20 examinations. In adults, on the contrary, a tuberculin reaction is almost always obtainable, so that it has little significance in relation to demonstrable lesions.

In table 6 the results of tuberculin tests have been arranged in three age groups in the order of their intensity when tested with quantities of tuberculin varying from 0.01 to 1 mgm., and for each grade of reaction the number of children with lesions recognized in roentgenograms is stated. Since there is no outstanding variation in relation to age, the percentage of recognizable pulmonary lesions with each grade of reaction is given at the bottom of the table.

TABLE 6

The relation of the tuberculin reaction to tuberculous lesions recognized by roentgenograms

AGE IN YEARS	NO TUBERCULIN REACTION		REACTION WITH 1 MGM.		REACTION WITH 0.1 MGM.		REACTION + WITH 0.01 MGM.		REACTION ++ WITH 0.01 MGM.		REACTION +++ OR ++++ WITH 0.01 MGM.	
	Number examined	With lesions of tuberculosis	Number examined	With lesions of tuberculosis	Number examined	With lesions of tuberculosis	Number examined	With lesions of tuberculosis	Number examined	With lesions of tuberculosis	Number examined	With lesions of tuberculosis
5–9	59	8	11	1	5	2	16	6	32	18	19	10
10–14	41	10	11	5	6	1	11	5	37	16	26	19
15–19	4	0	1	0	5	2	2	0	9	6	4	2
Total.....	104	18	23	6	16	5	29	11	78	40	49	31
Percentage with lesions of tuberculosis.....		17.3		26.1		31.2		37.9		51.3		63.3

With a negative tuberculin reaction 17.3 per cent have lesions with the characters of latent or manifest tuberculosis (pulmonary nodules, 15; lesions of tracheobronchial lymph nodes, 3). In some, if not in all, of these children a tuberculin reaction probably present during the early stage of tuberculous infection has later disappeared, for as mentioned

above, it is well known that the tuberculin reaction may disappear in both man and lower animals after recovery from tuberculosis. In two of these children a diagnosis of pulmonary tuberculosis was supported by physical signs and roentgenological evidence.

With positive reactions, increasing intensity of reaction is associated with gradually mounting frequency of recognizable tuberculous lesions, so that 63.3 per cent of children with the maximum grade of reaction (+++ and ++++ with 0.01 mgm.) exhibit lesions.

It is desirable to know what grade of reaction suggests grave tuberculous disease. Most instances of recognizable tuberculosis of tracheobronchial lymph nodes occur in children who give a positive reaction with 0.01 of tuberculin. Among 143 children who failed to react with this dose, 4 (2.7 per cent) had tuberculosis of tracheobronchial lymph nodes, whereas among 156 children who reacted with 0.01 mgm. 29 (18.6 per cent) had this lesion. Latent apical tuberculosis did not occur among those who failed to react with 0.01 mgm., but was present in 5 instances in children who reacted with this dose. Nevertheless, manifest tuberculosis occurred in both groups, but was more frequent in the second. The probability of grave tuberculous infection increases with the severity of the tuberculin reaction.

TUBERCULOSIS OF TRACHEOBRONCHIAL LYMPH NODES

This lesion has been identified with certainty in 48 instances (table 7), and its presence has been suspected in a considerable number of children. The age of the affected individuals has varied from 4 to 44 years, and in the following four instances the lesion has made its appearance while a child was under observation: *William Cl* (figs. 31, 32), 8 years; *Jack Cm*, 9 years; *Anna Mh* (figs. 23, 25), 12 years; and *Vincent Sd*, 12 years. In six instances tuberculosis of tracheobronchial lymph nodes has been recognized in adults, and although it is certain that the lesion is usually acquired in childhood it is probable that tuberculosis may assume this form in an individual who has escaped infection in early life. It was present in *Mary Ja* aged 40 years, who had been in contact with a tuberculous husband during 12 years, and in *Walter Je*, aged 44 years, in contact during 4 years with a tuberculous wife who died 3 years before his lesion was found.

Tuberculosis of tracheobronchial lymph nodes has occurred in almost all instances in association with prolonged exposure to open pulmonary tuberculosis. The incidence of the lesion in families with "sputum-

TABLE 7

Advanced tuberculosis of tracheobronchial lymph nodes

NAME	AGE WHEN FIRST SEEN	PROBABLE SOURCE OF INFECTION			MANIFEST TUBERCULOSIS	
		Relationship	Tubercle bacilli in sputum	Probable duration of contact	Age at onset	Character of lesion
				years		
Josephine Bc.	4	Father	+	4		
Florence Mh.	5	Father and mother	+	$3\frac{9}{12}$		
Josephine Ya.	5	Father	+	$4\frac{8}{12}$	5	Infantile type
Helen Zc.	5	Father	+	$4\frac{5}{12}$		
Robert Ca.	6	Mother and uncle	+	4		
David Dn.	6	(?)	−	−		
Elwood Ca.	7	Mother and uncle	+	4		
James Ck.	7	Father	+	7		
Willie Zc.	7	Father	+	$4\frac{5}{12}$		
William Cl.	8	Father	0	8		
Mendall Cl.	8	Father	0	$6\frac{11}{12}$		
Anna Ck.	8	Father	+	$9\frac{8}{12}$		
Elinore Jf.	8	Mother and grandmother	+	$1\frac{7}{12}$	8	Type not determined
Beatrice Ca.	9	Mother and uncle	+	4		
Jack Cm.	9	Sister	+	$3\frac{4}{12}$		
Clara Sf.	9	Mother	+	$1\frac{8}{12}$		
Abraham Sk.	9	Mother	+	$5\frac{8}{12}$		
Carmen Va.	9	(?)	−	−		
Rose Ac.	10	Mother and aunt	+	$4\frac{9}{12}$		
Anthony Sd.	10	Father	+	$3\frac{1}{12}$		
John Da.	11	Mother	+	$6\frac{8}{12}$	5	Pott's disease
Daniel Dk.	11	Brother	+	$2\frac{8}{12}$		
Katherine Ka.	11	Father and uncle	+	$2\frac{6}{12}$	5	Infantile type; arrested (?)

Anthony Sc	12	Father	+	3		Apical
Anna Ac	12	Mother and aunt	+	$4\frac{9}{12}$	14	Apical
Edward Ca	12	Mother and uncle	+	4		
Jennie Ia	12	Father	+	$7\frac{6}{12}$	13	Died from tuberculosis
Anna Mh	12	Father and mother	+	5	11	Apical
Vincent Sd	12	Father	+	3	11	Apical
Elizabeth Cb	13	Sister (?)	+	$\frac{7}{12}$ (?)		
Leo Ck	13	Father	+	9		
Catherine Ma	13	(?)	−	−	6	Type not determined
James Mg	13	Father	+	2		
Frances Mf	13	(?)	−	−		
Charlie Dh	14	Father	+	5		
Louis Me	14	Father	+	$6\frac{6}{12}$		
John Mh	14	Father and mother	+	5	14	Apical
Esther Mc	14	Mother	0	8		
Sarah Cl	14	Father	+	$8\frac{10}{12}$		
Amelia Dc	15	Mother (?)	0	(?)	11	Infantile type
John Mg	16	Father	+	$2\frac{1}{2}$		
Elizabeth Sl	18	Sister (?)	+	$\frac{6}{12}$ (?)	15	Apical; arrested
Margaret (Ka)Z	24	Father and uncle	+	$2\frac{6}{12}$	16	Apical
Anna Cf	30	(?)	−	−	24	Apical
Eva Gc	31	(?)	−	−		
Celia (Ac)M	38	(?)	−	−	(?)	Apical
Mary Ja	40	Husband (?)	+	−		
Walter Je	44	Wife (?)	+	$4\frac{3}{12}$		

positive tuberculosis" compared with "noncontact" families illustrates this relation (fig. 1). Of 41 instances of the lesion, in which the probable source of infection is known, all except 6 occurred in families in which the mother (12), or father (20), or both (3), had suffered with pulmonary tuberculosis. Particularly noteworthy is the frequency of the lesion (12 instances) in families of which two adult members have suffered with tuberculosis.

Long-continued exposure to tubercle bacilli discharged with the sputum is in most, if not in all, instances an essential factor in the production of this lesion, for of 41 instances in which the probable source of infection was known, tubercle bacilli had been found in the sputum of 37 by the routine methods of examination.

Analysis of the occurrence of latent tuberculous lesions among children exposed during various periods to open tuberculosis of a parent has shown that no tracheobronchial tuberculosis has occurred until the duration of exposure has been 3 years, and with this period of exposure only one instance has been found. After 4 years the incidence has been much higher, namely, 34.3 per cent of the children exposed during a period of from 4 to 5 years. In families, in which the duration of contact with open parental tuberculosis has been longer, the incidence of tracheobronchial tuberculosis has been much less, namely, 18.2 per cent after exposure during from 5 to 9 years and 10.5 per cent in children exposed during more than 9 years. In instances in which the duration of exposure has been more than 5 years it may be justly assumed that, in association with slowly progressive disease in the parent, fewer tubercle bacilli have been discharged with the sputum, so that whereas latent lesions have been approximately as frequent in the exposed children their severity has been less.

It has seemed desirable to examine the same relation from another point of view. The duration of contact with tuberculosis has been determined as accurately as possible. The average duration of contact in instances of tracheobronchial tuberculosis has been 4 years and 5 months. This figure may be accepted as the average period of exposure required to cause tuberculosis of the tracheobronchial lymph nodes so advanced that it may be recognized by roentgenological examination.

Clinical symptoms and physical signs have demonstrated the existence of manifest tuberculosis in 16 of the 48 instances of tracheobronchial tuberculosis which have been studied. The age at which manifest disease has made its appearance has varied much, ranging from five (*John*

Da, Catherine Ka (figs. 17, 18) and *Josephine Ya* (fig. 26)) to 24 years (*Anna Cf*), or even 37 years (*Celia M*, aunt of family *Ac* (figs. 9, 10)). In most instances symptoms have appeared in the latter half of childhood, but it is noteworthy that the study has included many children and but few young adults.

Anatomical studies have shown that lesions of the tracheobronchial lymph nodes are secondary to a tuberculous focus within the substance of the lungs and represent a first infection with tuberculosis. In association with the adult type of tuberculosis none of the usual changes of tuberculosis are found in the adjacent lymph nodes, and the disease limited to the lung tissue has the characters of a second infection with tuberculosis. With this distinction in view, the attempt has been made to determine whether manifest tuberculosis of the lung accompanying disease of tracheobronchial lymph nodes has the characters of tuberculosis of childhood or of adult life. Localization in one or both apices has been regarded as evidence of the adult type of the disease. In 9 instances the lesion has had this character, and has made its appearance in the latter half of childhood, that is, at 11 years of age or later. In 3 instances the lesion has had the characters seen in children, and has appeared twice in young children and in one at 11 years. In two instances (*Catherine Ma* and *Elinore Jf*) a lesion of infantile type has been present, but the apex has been implicated as well. In one instance death has occurred after appearance of tuberculosis at the age of 13 years, but the character of the disease has not been determined. Pott's disease has been associated with tracheobronchial tuberculosis in one instance.

In two children (*Anna Ac* (figs. 9, 10) and *Jennie Ia* (figs. 19, 20)) manifest tuberculosis made its appearance in children in whom tracheobronchial tuberculosis had been recognized two years before.

The frequent association of the tracheobronchial lesion, which represents a first infection, with apical tuberculosis, which usually occurs later in life and has the characters of a second infection, indicates that the lesion of the lymph node has preceded the appearance of the apical lesion. The recognition of tracheobronchial tuberculosis suggests the probability that manifest disease may later make its appearance. Since both lesions usually occur in families in which there has been prolonged contact with open tuberculosis, it is probable that the apical lesion is a superimposed exogenous infection occurring in an individual who is constantly receiving tubercle bacilli in great number. Resistance pre-

sumably conferred by the first infection is doubtless insufficient to prevent infection in the presence of massive dosage.

LATENT APICAL TUBERCULOSIS

In a small series of autopsies in which the distribution of latent tuberculous lesions was studied by one of us, latent apical tuberculosis was

TABLE 8

Latent apical tuberculosis

NAME	AGE	PROBABLE SOURCE OF CONTACT		
		Relationship	Tubercle bacilli in sputum	Probable duration of contact
	years			*years*
Rose Sc.	11	Father and uncle	+	8
Anna Sc.	13	Father and uncle	+	8
Adelaide Fg.	14	(?)	−	−
Mary Zc.	14	Father	+	4
Sarah Wa.	15	Mother	0	14
Jennie Wb.	15	Mother	0	$6\frac{9}{12}$
Helen (Ka)C.	21	Father and uncle	+	?
Antoinette Tb.	28	Husband	+	7
Margaret Ck.	31	Husband	+	9
Annie Bc.	33	Husband	+	4
Ida Si.	37	Husband (?)	0	2(?)
Joseph Ac.	38	Wife	+	7
Mary Dc.	40	(?)	−	−
Bessie Dh.	41	Husband	+	5
Mary Lb.	41	Brother	+	$7\frac{1}{12}$
Fannie Cl.	42	Husband	0	$8\frac{6}{12}$
Mary Ja.	42	Husband	+	$10\frac{5}{12}$
Susie Ia.	49	Husband	+	$8\frac{4}{12}$
Cain Db.	50	Wife	0	12
Frances Bh.	56	(?)	−	−
Tony Do.	58	(?)	−	−
Mary Ia.	69	(?)	−	−

present in one of five of those examined. This figure is not an accurate measure of the frequency of the lesion in adults who die from diseases other than tuberculosis, for the incidence of the lesion has varied with age, increasing from early adult life to old age, so that in those over 50 years of age at death 28.5 per cent have had caseous or calcified lesions of the apex, which have caused no noteworthy symptoms. Although these figures demonstrate the frequency of latent apical tuber-

culosis, they give no exact information concerning its frequency in the general population.

By means of stereoscopic roentgenograms, lesions with the characters of those found at autopsy may be recognized (see p. 353). We have excluded instances in which interpretation of films has been doubtful. Doubtless, occasionally a lesion is hidden by the uppermost ribs, and it is probable that we have failed to recognize some lesions which have been present.

Latent apical tuberculosis has been found in 22 instances and these are arranged in sequence of age in table 8. When the lesion has occurred in adolescent children and in young adults, the probable source of contact has been one or the other parent, whereas in older individuals the probable source of contact has been husband or wife. In several adults no information concerning the probable source of infection could be obtained.

In a large part of those with known sources of infection (12 of 17) there had been prolonged contact with a tuberculous individual discharging tubercle bacilli in the sputum. In a few instances the individual with latent apical disease had lived with a tuberculous parent or with a consort whose sputum contained, when examined, no tubercle bacilli. Nevertheless, it is not improbable that tubercle bacilli may have been discharged intermittently.

With only one exception (*Ida Si*), in which the duration of contact is uncertain, the period of exposure has been four or more years, and the average duration of exposure has been 7 years and 11 months. It is noteworthy that this is nearly twice as long as the average period of exposure required to produce recognizable tracheobronchial tuberculosis.

Apical lesions have been regarded as latent when they have been unaccompanied by symptoms or physical signs recognized by patient or physician. In accord with this definition, there can be no sharp separation between latent and manifest disease. There has been little opportunity to determine whether, with latent apical tuberculosis, tubercle bacilli are discharged with the sputum. Nevertheless, in view of the character of latent lesions, which are occasionally associated with advanced caseation, it is not improbable that discharge of bacilli by way of the bronchi may occur at times. In several instances it is probable that an adult with latent apical tuberculosis, acting as an infecting carrier, has transmitted tuberculosis to children of the household. In family *Do* the mother suffered with far-advanced open tuberculosis, and

both children who were highly sensitive to tuberculin exhibited focal pulmonary lesions. The paternal grandfather, aged 58 years, who had lived in the household during ten years, had had no symptoms indicative of pulmonary tuberculosis, but when examined in the routine investigation of the family was found to have a left apical lesion implicating one-third of the lung together with a less advanced lesion of the right lung. In family *Dc* the oldest child had tracheobronchial lesions together with clinically recognizable tuberculosis, the next child had a focal pulmonary lesion, and the two youngest children gave active reactions with tuberculin. The mother, aged 40 years, exhibited an apical lesion, although she had had no symptoms suggestive of tuberculosis. The evidence available is insufficient to prove that the grandfather in one instance or the mother in the other had infected other members of these families, but it suggests the desirability of further study to determine whether certain individuals with latent apical tuberculosis discharge tubercle bacilli from the lungs and act as infecting carriers of the tubercle bacillus.

The occurrence of latent apical lesions in adolescent children will be discussed in association with manifest tuberculosis.

MANIFEST TUBERCULOSIS

Instances of manifest tuberculosis which have occurred in the children of families under observation fall into three groups: (1) Well-established tuberculosis has occurred in individuals who have not been examined by us and, with few exceptions, they have died before our study of the family had been undertaken. Evidently these instances will give little information about morbidity from tuberculosis in the families concerned, for even more frequently, particularly with young children, a doubtful history suggests that death occurred as the result of tuberculosis, but decisive evidence is not obtainable. (2) Tuberculosis confirmed by our examination had made its appearance in children of families in which no adult has suffered with the disease. Infection has occurred outside of the family, but the present study has not afforded means of tracing its origin. These children have been brought to the dispensary for the treatment of existing disease and have not, like the children of the next group, come under observation because an adult member of the family suffered with pulmonary tuberculosis. There have been 4 children and one adult in which the source of infection has been uncertain. In two instances it is probable that the mother has transmitted the disease.

These are *Amelia Dc*, whose mother has a latent apical lesion, and *Alfred Md*, whose mother died with tuberculosis when he was aged 5 years. (3) Tuberculosis has appeared in families of which an adult member suffering with tuberculosis has been the probable source of infection. In the relatively small group of families in contact with open tuberculosis in a parent, manifest tuberculosis has been recognized by us eleven times (fig. 1), and in several instances has been present in children whom we were not able to examine. In the group of families in which one child has suffered with open tuberculosis a second child has become tuberculous only once. In families with tuberculosis in parent or child and sputum negative for tubercle bacilli, no manifest tuberculosis has appeared in other members of the family.

With manifest tuberculosis the known period of contact has varied from 1 year and 7 months to 9 years. When a parent has been the source of infection the average duration of contact has been 4 years and 7 months. In one family (*Family Sl*) the oldest daughter exhibited symptoms of tuberculosis, and after nine months the second daughter had physical signs of pulmonary tuberculosis. It is not possible to determine whether one was infected by the other, or whether both acquired the disease outside of the family, perhaps from the same individual.

The age of onset of manifest tuberculosis has varied from five years (3 instances) to 23 years (1 instance), but in most cases the disease has made its appearance in the later period of childhood between 11 and 16 years of age. Roentgenological examination in some instances does not determine with certainty whether the lesion which causes symptoms has the characters of the infantile or of the adult type of tuberculosis, for there has been widespread disease of the lung, including the apex. In all but one instance focal pulmonary tuberculosis has been recognizable, and with few exceptions advanced tuberculosis of tracheobronchial lymph nodes has been found (13 of 17 instances). When the associated pulmonary lesion recognized by roentgenological examination has the character of diffuse infiltration not definitely localized in the apex, it is probable that tuberculosis of infantile type is responsible for existing symptoms. Nevertheless, calcified lesions of lymph nodes associated with focal pulmonary tuberculosis, representing a first infection, may be accompanied by the adult type of tuberculosis which, arising in the apex, has the characters of a second infection. Examination of table 9 shows that the infantile type of tuberculosis has usually been present when

TABLE 9

Manifest tuberculosis of childhood and adolescence

NAME	AGE AT ONSET	PRESENT AGE	CHARACTER OF MANIFEST TUBERCULOSIS	ASSOCIATED TUBERCULOSIS OF LUNGS	PROBABLE SOURCE OF INFECTION		
					Relationship	Tubercle bacilli in sputum	Probable duration of contact
	years	*years*					*years*
John Da	5	12	Pott's disease	Lymph node	Mother	+	$6\frac{8}{12}$
Katherine Ka	5	11	Infantile type; arrested (?)	Lymph node	Father and uncle	+	$2\frac{6}{12}$
Josephine Ya	5	6	Infantile type	Lymph node	Father	+	$4\frac{6}{12}$
Catherine Ma	6	13	Not determined	Lymph node	(?)	−	−
Elinore Jf	8	10	Not determined	Lymph node	Mother and grandmother	+	$1\frac{7}{12}$
Amelia Dc	11	17	Infantile type	Lymph node	Mother (?)	−	−
Anna Mh	11	14	Apical	Lymph node	Father and mother	+	5(?)
Vincent Sd	11	14	Apical	Lymph node	Father	0	3
Anna Ac	14	15	Apical	Lymph node	Mother	+	$7\frac{8}{12}$
Celia Cm	14	19	Infantile type; arrested (?)	Nodule	(?)	−	−
Jennie Ia	14	Died		Lymph node	Father and brother	+	$8\frac{6}{12}$
John Mh	14	16	Apical	Lymph node	Father and mother	+	5(?)
Josephine Ea	15	15	Apical	Nodule	Father	+	7(?)
Alfred Md	15	18	Apical	Nodule	Mother (?)	−	−
Elizabeth Sl	15	19	Apical; arrested	Lymph node	Sister	+	
Margaret (Ka)Z	16	24	Apical: arrested	Lymph node	Father and uncle	+	$2\frac{6}{12}$
Rose Sl	23	26	Not determined; arrested		(?)	−	−

manifest tuberculosis has had its onset in early childhood, whereas in older children physical signs and symptoms have been referable to apical tuberculosis.

There is no evidence that tracheobronchial tuberculosis causes apical disease by extension into the lung substance or otherwise. The lymphatic lesion is often on one side, and apical disease on the other. Focal pulmonary tuberculosis with associated disease of tracheobronchial lymph nodes, occurring in families with open tuberculosis, has made its appearance in consequence of long-continued exposure to tuberculosis, usually in crowded homes and occasionally with undernutrition enforced by poverty. Continued exposure to the same conditions furnishes a plausible explanation of subsequent apical disease, for resistance conferred by a first infection has been insufficient to protect against tubercle bacilli in massive dosage.

MARITAL TUBERCULOSIS

Latent apical tuberculosis occurring in husband or wife exposed to open tuberculosis of the consort proves that tuberculous infection may be acquired during adult life. Figure 1 shows the incidence of manifest and latent apical tuberculosis in the parents of 34 families, in which mother or father, or both, suffered with open tuberculosis. In three instances both parents have suffered with manifest disease, and in two of these families both husband and wife have had tubercle bacilli in the sputum. In 7 families latent apical lesions have been found in the consort of one or other parent who has suffered with open tuberculosis. In 11 other families examination of the consort of a tuberculous individual has failed to demonstrate an apical lesion, and in the remaining families examination of the consort with no manifest tuberculosis has not been possible. In approximately one-half (10 of 21) of the families in which both parents were examined there has been manifest or latent apical tuberculosis in both husband and wife.

The incidence of latent apical tuberculosis in 33 families with no manifest tuberculosis (figure 1) differs widely from that in families with open tuberculosis in a parent. In 13 parents examined latent apical tuberculosis has been found once. This figure is in agreement with the result of examinations of a larger number of adults made subsequently.

In 13 families, in which one or other parent has suffered with tuberculosis demonstrable by physical signs and roentgenological examination, but with no tubercle bacilli in the sputum, latent apical disease has

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Manifest tuberculosis of childhood and adolescence

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					Relationship	Tubercle bacilli in sputum	Probable duration of contact
	years	*years*					*years*
John Da	5	12	Pott's disease	Lymph node	Mother	+	$6\frac{8}{12}$
Katherine Ka	5	11	Infantile type; arrested (?)	Lymph node	Father and uncle	+	$2\frac{6}{12}$
Josephine Ya	5	6	Infantile type	Lymph node	Father	+	$4\frac{6}{12}$
Catherine Ma	6	13	Not determined	Lymph node	(?)	−	−
Elinore Jf	8	10	Not determined	Lymph node	Mother and grandmother	+	$1\frac{7}{12}$
Amelia Dc	11	17	Infantile type	Lymph node	Mother (?)	−	−
Anna Mh	11	14	Apical	Lymph node	Father and mother	+	5(?)
Vincent Sd	11	14	Apical	Lymph node	Father	0	3
Anna Ac	14	15	Apical	Lymph node	Mother	+	$7\frac{8}{12}$
Celia Cm	14	19	Infantile type; arrested (?)	Nodule	(?)	−	−
Jennie Ia	14	Died		Lymph node	Father and brother	+	$8\frac{6}{12}$
John Mh	14	16	Apical	Lymph node	Father and mother	+	5(?)
Josephine Ea	15	15	Apical	Nodule	Father	+	7(?)
Alfred Md	15	18	Apical	Nodule	Mother (?)	−	−
Elizabeth Sl	15	19	Apical; arrested	Lymph node	Sister	+	
Margaret (Ka)Z	16	24	Apical: arrested	Lymph node	Father and uncle	+	$2\frac{6}{12}$
Rose Sl	23	26	Not determined; arrested		(?)	−	−

manifest tuberculosis has had its onset in early childhood, whereas in older children physical signs and symptoms have been referable to apical tuberculosis.

There is no evidence that tracheobronchial tuberculosis causes apical disease by extension into the lung substance or otherwise. The lymphatic lesion is often on one side, and apical disease on the other. Focal pulmonary tuberculosis with associated disease of tracheobronchial lymph nodes, occurring in families with open tuberculosis, has made its appearance in consequence of long-continued exposure to tuberculosis, usually in crowded homes and occasionally with undernutrition enforced by poverty. Continued exposure to the same conditions furnishes a plausible explanation of subsequent apical disease, for resistance conferred by a first infection has been insufficient to protect against tubercle bacilli in massive dosage.

MARITAL TUBERCULOSIS

Latent apical tuberculosis occurring in husband or wife exposed to open tuberculosis of the consort proves that tuberculous infection may be acquired during adult life. Figure 1 shows the incidence of manifest and latent apical tuberculosis in the parents of 34 families, in which mother or father, or both, suffered with open tuberculosis. In three instances both parents have suffered with manifest disease, and in two of these families both husband and wife have had tubercle bacilli in the sputum. In 7 families latent apical lesions have been found in the consort of one or other parent who has suffered with open tuberculosis. In 11 other families examination of the consort of a tuberculous individual has failed to demonstrate an apical lesion, and in the remaining families examination of the consort with no manifest tuberculosis has not been possible. In approximately one-half (10 of 21) of the families in which both parents were examined there has been manifest or latent apical tuberculosis in both husband and wife.

The incidence of latent apical tuberculosis in 33 families with no manifest tuberculosis (figure 1) differs widely from that in families with open tuberculosis in a parent. In 13 parents examined latent apical tuberculosis has been found once. This figure is in agreement with the result of examinations of a larger number of adults made subsequently.

In 13 families, in which one or other parent has suffered with tuberculosis demonstrable by physical signs and roentgenological examination, but with no tubercle bacilli in the sputum, latent apical disease has

been found twice in the consort with no manifest disease. It has been possible to examine the apparently healthy consort in only 3 other families of this group, so that of those examined 2 of 5 adults associated with tuberculous consorts had latent apical lesions.

Statistical studies of marital tuberculosis have had widely different results, and the possible fallacies in their interpretation have been repeatedly discussed. Some of those who have studied the problem (Fishberg (14)) find no evidence of marital infection; but a greater number, for example, Barnes (15), have found that tuberculosis occurs more frequently in the consorts of tuberculous individuals than in the general population, although the preponderance is not great. Statistics based upon many thousands of couples have been collected from the literature of the subject and analyzed by exact mathematical methods in the well-known study of Pope and Pearson (16). More recently, statistics based upon 53,069 couples, of which husband or wife suffered with tuberculosis, have been collected by Arnould (17), and in 4,472 instances both have been found tuberculous, namely 8.43 per cent. Arnould reaches the conclusion that there is a definite increase of tuberculosis as the result of marital contact, but it does not exceed by more than half the morbidity of the general population.

When latent apical tuberculosis is taken into consideration, more accurate insight into marital contagion is obtained. The study of our families, even though the number of individuals concerned is very small, shows that the healthy consort of a tuberculous individual may become infected. The resulting lesion is usually limited to a small part of the apex, and has little tendency to spread, so that in most instances it causes no evident disturbance of health. Nevertheless, examination of the small group of individuals who have come under observation shows that the lesion varies in extent from an inconspicuous apical cap to massive infiltration implicating the upper third of a lung, and finally to progressive disease obvious to physician and to patient.

Manifest tuberculosis of the consort of a tuberculous parent has been found twice with tubercle bacilli in the sputum and once with no tubercle bacilli. When the disease becomes manifest there is no means of determining how long it has been latent. Newsholme (18) has found that there is usually a long latent period, often 10 or more years, between exposure and infection and appearance of symptoms of phthisis. It is probable that this period of latency tends to diminish the frequency with which manifest tuberculosis is discovered in consorts of tuberculous individuals.

TUBERCULOSIS OF ADOLESCENCE AND EARLY ADULT LIFE

The frequency of tuberculosis in early adult life has received no adequate explanation, although the prevention of this manifestation of the disease is the most important factor in the control of tuberculosis. The foregoing observations have shown that latent infection precedes much of the manifest disease which makes its appearance in childhood. Recognizable tuberculosis of the tracheobronchial lymph nodes, which itself causes no distinctive symptoms or physical signs, may precede or accompany manifest tuberculosis in children. In early childhood the associated manifest disease conforms to the infantile type of pulmonary tuberculosis, whereas in the later period of childhood, namely, during the second decade, the lesion in most instances resembles the phthisis of adults. There may be cough, loss of weight, cavity formation and tubercle bacilli in the sputum, but just as often the child suffers no inconvenience from the disease which has been recognized by physical signs. In some adolescent children (*Anna Ac* (figs. 9, 10), *Josephine Ea* and *Anna Mh* (figs. 23, 25)) widespread infiltration of the apex has been recognized in roentgenograms and has been associated with apical râles, but the patient has been well nourished and apparently in excellent health. These lesions have occurred in families of which one patient has long suffered with open tuberculosis, and have doubtless been caused by continued exposure to infection with tubercle bacilli in great quantity.

There is no sharp separation between these instances of manifest disease and lesions designated as latent apical tuberculosis. In one instance physical signs have been present and in the other none have been found. Examples of latent apical tuberculosis with widespread infiltration of the apex occurred in *Sarah Wa* (figs. 33, 34), *Anna Sc* (figs. 29, 30) and *Mary Zc* (figs. 27, 28), all of whom are older children of families in which a parent suffered with tuberculosis.

Little is known concerning the conditions under which latent apical lesion assumes the character of manifest disease. In some instances apical tuberculosis in young adults (*Alfred Md* aged 18 years, *Margaret (Ka)Z* (figs. 17, 18) aged 24 years) has been evident since adolescence. In other instances doubtless the disease has remained masked during a considerable period of years.

In one group of adolescent children, which have been seen by us, tuberculosis has caused no noteworthy disturbance of health, and un-

recognized by physical signs would have remained undiscovered if these patients had not been examined during the course of our study. In another group with latent tuberculosis the apical lesion has been as extensive as that with physical signs. We have cited the observations of Newsholme, which show that a period of several years usually intervenes between exposure to infection, measurable only when exposure ceases, and appearance of symptoms of phthisis. These considerations indicate that unrecognized pulmonary tuberculosis, which has had its origin during adolescence, may later manifest itself during early adult life. It is noteworthy that the lesion which appears during adolescence, and progressing becomes the phthisis of adult life, has the characters of a second infection.

PREDICTION OF MANIFEST TUBERCULOSIS

The need for means by which manifest tuberculosis may be predicted requires little emphasis. Tuberculosis recognized soon after the appearance of symptoms is usually curable, and there can be little doubt that tuberculosis recognized before the appearance of symptoms can be placed under conditions which in most instances will ensure complete healing. In the foregoing study the attempt has been made to determine the conditions under which latent becomes manifest disease. It is desirable to know whether this information will serve as an index of probable disease.

Manifest tuberculosis may be anticipated in a considerable part of the children of families in which there has been open tuberculosis, and the probable morbidity will increase with the period of exposure. Our figures indicate that at least 1 in 11 of the exposed children will suffer with tuberculosis; but this estimate is doubtless far below the true number, for the families concerned have been under observation only three years and, although it includes many instances of manifest tuberculosis which have appeared before the period of observation, other children, particularly the younger members of families, will later develop the disease.

In the small group of families in which there has been recognizable tuberculosis, although no tubercle bacilli have been demonstrable in the sputum, no manifest tuberculosis has occurred in the children, but since latent tuberculosis, especially tracheobronchial and latent apical disease, is more common in this group than in noncontact families, it cannot be assumed that manifest disease will not occur.

When manifest tuberculosis makes its appearance in the children of a family in which no other members have suffered with it a second child may subsequently exhibit the disease. It is possible that the first has infected the second, but almost simultaneous appearance of symptoms in the two children may indicate that both have been infected from some source outside of the family.

The foregoing considerations emphasize the gravity of contact with open tuberculosis and show that the danger during at least four years increases with the duration of exposure (see p. 373).

Much experimental and other evidence has shown that the tuberculin reaction is an index of tuberculous infection, and observations of Baldwin (19), Krause (20) and others indicate that the cutaneous reaction does not occur in the absence of anatomical tubercle. In association with the present study it is important to determine whether it may be used as an index to latent tuberculosis recognizable by roentgenological examination, and especially whether it may be used to select latent infections which threaten manifest disease.

It is well known that the tuberculin reaction is occasionally absent in association with evident tuberculosis, and in two instances of manifest tuberculosis in families under observation there has been no skin reaction with 1 mgm. of tuberculin. It is possible that a larger amount would have produced a reaction (see Happ and Casparis).

Tests with decreasing quantities of tuberculin (see table 6) show that there is a close but not exact correlation between sensitiveness to tuberculin and the occurrence of lesions so conspicuous that they are recognizable by roentgenograms. It is noteworthy that lesions quite as extensive as those which are recognized are occasionally overlooked because, on the one hand, they are hidden by opaque structures or, on the other hand, have undergone no calcification.

With a negative tuberculin reaction one in six children exhibits roentgenological evidence of tuberculous infection. When 1 mgm. of tuberculin is required to produce a skin reaction, 1 in 4 (26.1 per cent) have tuberculous lesions demonstrable by roentgenological examination and, of children sensitive to 0.1 mgm., 1 in 3 have demonstrable lesions. Among those who react with 0.01 mgm. the frequency of lesions increases with the intensity of the reaction, namely with one plus, over one-third of those tested (37.9 per cent); with two plus, over half (51.3 per cent) and with three and four plus almost two-thirds (60 to 64.7 per cent).

Children who react with 0.01 mgm. of tuberculin will include a large

proportion of those in whom lesions are demonstrable by roentgenograms, for of 111 demonstrable lesions three-fourths (73.9 per cent) have occurred in those who have exhibited a positive tuberculin reaction with tuberculin in this amount. Furthermore, these children have included approximately nine-tenths (87.9 per cent) of those who have had recognizable tuberculosis of tracheobronchial lymph nodes. Furthermore, they included all children in whom latent apical tuberculosis has been demonstrable; indeed with latent apical tuberculosis all children have had a reaction designated two, three or four plus with 0.01 mgm. of tuberculin.

Tracheobronchial tuberculosis recognized by roentgenological examination has been present in most instances of manifest tuberculosis, and during the short period of observation manifest tuberculosis has in several instances made its appearance in children in whom the tracheobronchial lesion had previously been demonstrated. Ghon and others have found a pulmonary focus, regarded by them as primary, with few if any exceptions associated with tuberculosis of tracheobronchial lymph nodes. This relation is characteristic of the infantile type of tuberculosis, for one of us has shown that phthisis of adults and the closely related latent apical lesions are not accompanied by tuberculosis of lymph nodes at the hilum of the corresponding upper lobe. Evidence which shows that the apical tuberculosis of adults is a second infection not derived from the preëxisting lesion which implicates the tracheobronchial lymph nodes has been discussed. In table 7 are listed 15 instances in which recognizable tracheobronchial tuberculosis has been associated with manifest pulmonary disease. In two instances, namely, *Anna Ac* (figs. 9, 10) and *Jennie Ia* (figs. 19, 20), tuberculous lymph nodes were recognizable before manifest tuberculosis made its appearance. In the following instances calcified lymph nodes representing a first infection doubtless preceded manifest apical disease: *Anna Ac*, *Anthony Sc*, *Vincent Sd*, *Anna Mh*, *John Mh*, *Elizabeth Sl* and *Margaret* (*Ka*)*Z* (see figures). The foregoing evidence shows that recognizable tracheobronchial tuberculosis in children has grave significance, and may serve as an index of manifest disease.

How frequently apical tuberculosis unassociated with symptoms or physical signs later gives rise to manifest disease is not yet evident, but the separation is often artificial. It has been pointed out that latent lesions are occasionally less advanced than those which cause symptoms, and neither roentgenological examination nor anatomical study serves

to distinguish one from the other. Latent apical tuberculosis has been found repeatedly in adolescent children and in young adults. Apical tuberculosis with no history of symptoms, but accompanied by apical râles, has been found by roentgenological examination in adolescent children who are well nourished and apparently healthy. In other instances apical tuberculosis in adolescent children has been accompanied by the usual symptomatology of phthisis. It is evident that latent apical tuberculosis in adolescent children may precede manifest disease of early adult life. Indeed, it is not improbable that much of the tuberculosis of this period has its origin in latent apical disease acquired during adolescence as the result of exposure to massive infection in the home. The discovery of latent apical tuberculosis in an adolescent child suggests that manifest disease may develop during early adult life.

CONTROL OF TUBERCULOSIS IN THE FAMILY

Our study has shown that dispensaries for the treatment and prevention of tuberculosis should be formally organized to care for the families of all their tuberculous patients. Routine procedures should not only determine the existence of evident disease, but should measure the progress and severity of latent infection. A chart such as that which we have described, constructed to show how long each member of the household has been exposed to the danger of infection and the results of this contact, is essential to an adequate realization of the progress of infection within a family. In addition to the usual methods for recognition of the disease, routine quantitative tuberculin tests at intervals of one year are essential and, as far as facilities permit, roentgenological examinations of all exposed individuals must be made in order to determine the nature and severity of hidden infection. The interpretation of tuberculin tests will depend upon the age of the child and the severity of the reaction (see p. 363). The significance of lesions discovered by roentgenograms will be determined by their position and extent, but here again the age of the individuals concerned must be taken into consideration (see p. 361).

An examination of a series of charts, depicting families in contact with open tuberculosis during several years, will disclose instances in which every member has intense sensitiveness to tuberculin and, upon roentgenological examination, exhibits lesions of tuberculosis. The severity of infection bears a close, if not accurate, relation to the size and position of these lesions, conspicuous latent lesions of tracheobronchial lymph

nodes and of pulmonary apices having graver significance than circumscribed nodules within the substance of the lung elsewhere. In these families infection has evidently attained great severity, and along with this latent infection instances of manifest disease will probably make their appearance. After the first two years of life there is a long age-period during which morbidity is low, but among adolescent children manifest disease increases with age. In families consisting of younger children harboring the severer types of infection a high incidence of manifest disease may be predicted. In the families in which there has been prolonged contact with open tuberculosis, transfer of infection to adults is by no means negligible. Marital contagion is demonstrable in approximately one-half of them, and the probable transition from latent apical tuberculosis to manifest phthisis cannot be ignored. Examples of families "saturated" with tuberculous infection are families *Ac*, *Bc*, *Ca*, *Ck*, *Dh*, *Do*, *Ea*, *Ia*, *Je*, *Ka*, *Mg*, *Mh*, *Sc*, *Ya* and *Zc* (fig. 1, etc.).

Charts such as those just cited should be carefully studied by all who are interested in municipal or other governmental control of tuberculosis. Humanitarian considerations suggest the desirability of restraining further dissemination within the family, even if danger to others should be forgotten. From the standpoint of economy, funds available for the control of the disease being limited, it might well prove desirable for health authorities to assume responsibility for severely infected families, to care for those who suffer with disease, and to place all others under such favorable conditions that latent will not produce manifest tuberculosis.

The foregoing statements refer to families of which some member suffers with open tuberculosis. Observations made upon families, in which contact with tubercle bacilli has varied in intimacy and duration, have shown that evidence of latent and manifest infection shows corresponding variation. It has become evident that widespread tuberculosis in the children of a family may serve as an index of exposure to contagion. In certain families with no obvious contact with tuberculosis multiple and severe latent infections, especially in younger children, have suggested exposure to the disease. In family *Cl* (figs. 31, 32) three children, varying in age from 7 to 14 years of age, exhibited tracheobronchial tuberculosis, developing in two instances during the period of observation, and in the remaining child a pulmonary nodule was discovered. Examination showed that both the mother and the father had inconspicuous apical lesions, that of the father being accom-

panied by evident symptoms. In family *Kb* latent tuberculosis in children directed attention to the disease in the mother.

The occurrence of latent focal and tracheobronchial tuberculosis in children of families *Dn* and *Mf* (fig. 1), classified as "noncontact" families, suggests that they have been exposed to tuberculosis, but no history of contact has been obtainable.

When this reversal of the usual order of inference has been applied to the group of families in which exposure to infection is uncertain (families with possible contact, see p. 359) occurrence of latent tuberculosis in several children of the household may suggest that the individual suspected of tuberculosis at one time discharged tubercle bacilli. Confirmatory evidence of contact with tuberculosis was found in families *Bg*, *Ha*, *Si* and *Wd*. In other families, namely, families *Sb* and *Fd*, absence of evident infection, except in the older children of the former, tends to support the assumption that there has been no open tuberculosis in the family. Conclusions from this form of inference are subject to reservation.

It is inadvisable to assume that infected children of families with open tuberculosis are protected from subsequent infection. Increased severity of latent lesions associated with prolonged contact indicates that the acquired resistance is an insufficient safeguard against massive infection. Even though all members of a family are infected, it is desirable to separate the phthisical patient scattering tubercle bacilli from the home or, if this measure is impracticable, to teach the patient and other members of the household those well-known procedures which diminish the danger of infection.

Latent tuberculosis under certain readily definable conditions so frequently gives rise to manifest disease that it must be regarded as a grave menace to the individual. Since tuberculosis recognized by symptoms and physical signs in the earlier phases of its development is usually amenable to treatment by rest and diet, tuberculosis recognized before symptoms and physical signs are evident is doubtless even more readily arrested. Latent tuberculosis which foreshadows manifest disease is indicated by a tuberculin reaction in a child less than two years of age, by tuberculosis of tracheobronchial lymph nodes demonstrable by roentgenograms, and by latent apical disease recognized by the same means. In such instances physical examination repeated at short intervals and roentgenograms, made at intervals not greater than 6 months, will determine whether the disease is progressing. Sufficient diet and

measures directed to prevent fatigue are needed. Open-air schools and camps maintained in the country are especially desirable for this group of children, and in some instances sanatorium treatment may be suitable. Children with recognizable tracheobronchial tuberculosis and adolescent children, or adults with latent apical disease, should receive the care given to patients with recently arrested phthisis.

CONCLUSIONS

1. When latent tuberculosis is taken into consideration, tuberculosis exhibits the characters of a contagious disease and affects all children of households within which some member, suffering with tuberculosis, scatters tubercle bacilli.

2. Recognition of latent apical tuberculosis has demonstrated that tuberculous infection is transmitted to adults and to adolescent children, and has shown that approximately one-half of the partners of husbands and wives with open tuberculosis are infected after marriage.

3. Duration of exposure to open tuberculosis is an important factor in determining the character and severity of the resulting infection; in instances of recognizable tuberculosis of tracheobronchial lymph nodes the average duration of contact with tuberculosis has been approximately four and a half years, and in instances of latent apical tuberculosis nearly twice as much.

4. Dispensaries for the care and control of tuberculosis should be organized so that spread of latent infection within the family may be recognized and prevented. A chart for each family, depicting the severity of latent and manifest disease disclosed by quantitative tuberculin reactions and roentgenological examination, will forcibly direct attention to effective means of control.

5. Latent tuberculosis often becomes manifest. Certain forms of latent infection foretell the approach of clinically recognizable disease. These are (1) infection recognizable by the tuberculin reaction during the first two years of life, (2) tracheobronchial tuberculosis in children recognized by roentgenological examination, and (3) latent apical tuberculosis in adolescent children. Children with these forms of tuberculous infection should be examined at frequent intervals, and treated as though they had recently arrested tuberculosis.

6. All adults in whom latent apical tuberculosis has been recognized should receive the same care as patients with arrested phthisis.

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Explanation of Figures 3 to 36

Family charts depict the distribution of tuberculosis in families, and diagrams show important lesions found in roentgenograms of members of these families. Brief clinical notes explain the progress of the disease in each family. The method of charting is described on page 349. Tuberculin reactions are indicated by 0 (negative), or from one to three plus signs over the quantity in milligrams of tuberculin used. Symbols are used to indicate tuberculous lesions. A heavy black dot at the left of the life-line represents a focal tuberculous lesion of the lung; an encircled dot is tracheobronchial tuberculosis; an arc with a salient projecting downward is latent apical tuberculosis. A cross upon the life-line indicates that roentgenological examination has been made at the date indicated with negative result. A heavy black column at the right of the life-line indicates manifest tuberculosis; an additional column on the left indicates that the sputum contained tubercle bacilli. The result of sputum examination (*Sp*) is indicated by zero or plus placed above the number of examinations. A series of dots on the right of the life-line indicates that tuberculosis has been suspected.

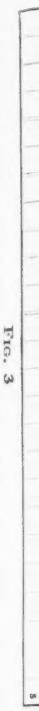


Fig. 3

Figure 3

Family Gd: There is no known contact with tuberculosis. Ida has mitral regurgitation and has had chorea. *Housing:* Six rooms and bath for six persons. *Cleanliness:* Fair. *Diet:* Sufficient. *Financial status:* Fair.

Figure 4

Family Sa: The father died of influenza in 1918. There is no known contact with tuberculosis. *Housing:* Four rooms for seven persons. *Cleanliness:* Fair. *Diet:* Sufficient in quantity but low in protein. *Financial status:* Poor.

Remarks: The only evidence of tuberculous infection is a positive tuberculin reaction in the oldest child and this after approximately two years has diminished in intensity.

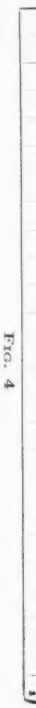


Fig. 4

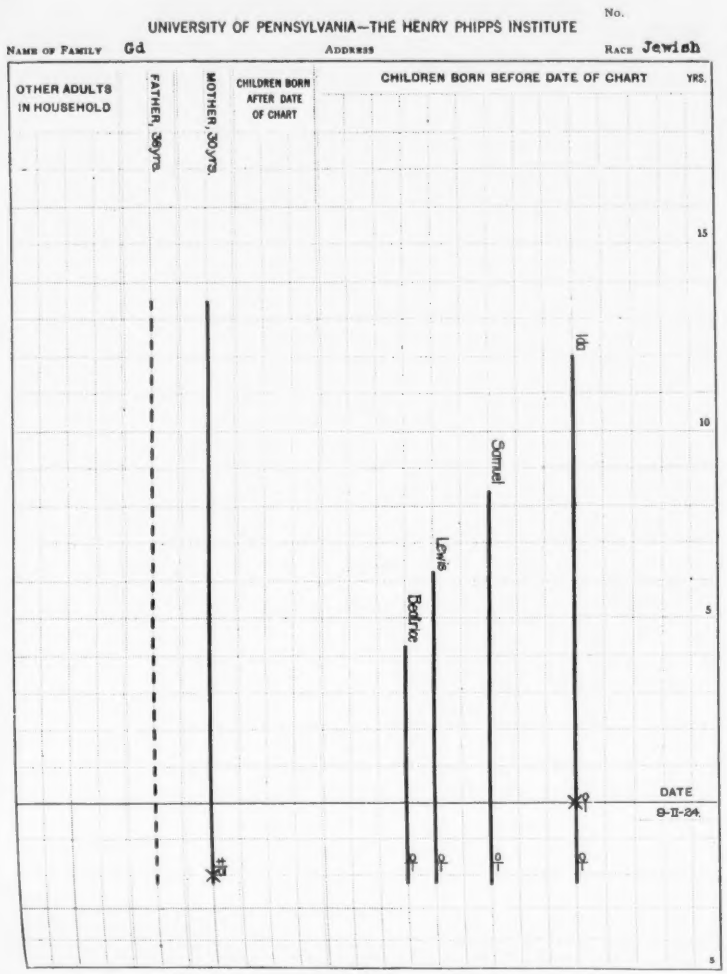

No.
UNIVERSITY OF PENNSYLVANIA—THE HENRY PHIPPS INSTITUTE
NAME OF FAMILY Gd
ADDRESS
RACE Jewish
OTHER ADULTS IN HOUSEHOLD
FATHER, 36yrs.
MOTHER, 30yrs.
CHILDREN BORN AFTER DATE OF CHART
CHILDREN BORN BEFORE DATE OF CHART
YRS.
15
10
5
Beatrice
Lewis
Samuel
Ida
DATE
9-II-24.

FIG. 3

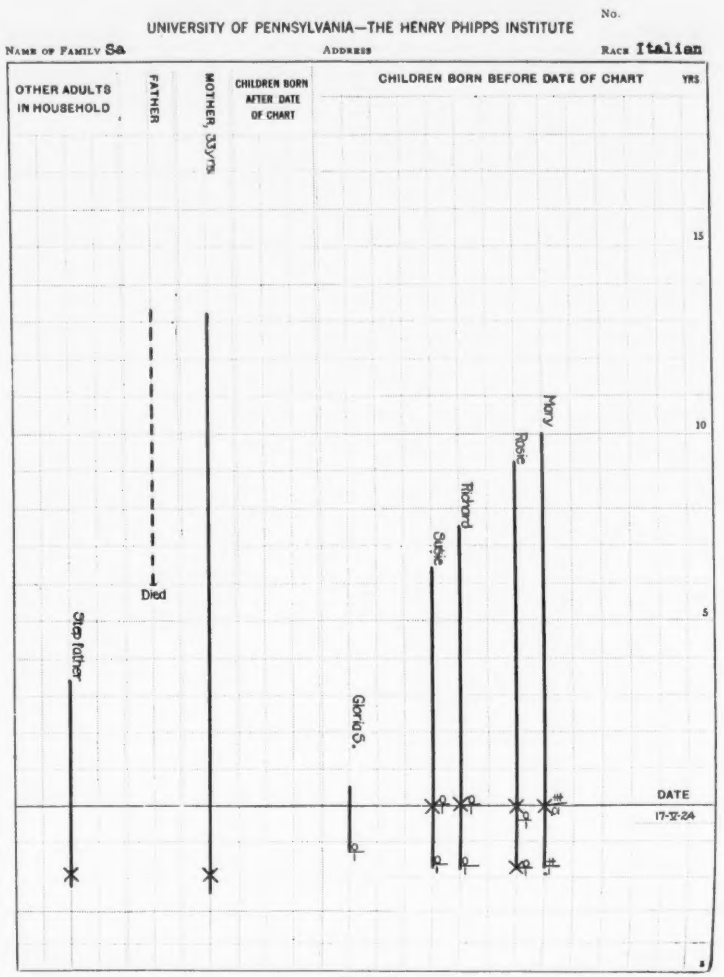

No.
UNIVERSITY OF PENNSYLVANIA—THE HENRY PHIPPS INSTITUTE
NAME OF FAMILY Sa
ADDRESS
RACE Italian
OTHER ADULTS IN HOUSEHOLD
FATHER
MOTHER, 33yrs.
CHILDREN BORN AFTER DATE OF CHART
CHILDREN BORN BEFORE DATE OF CHART
YRS.
15
10
5
Step father
Died
Gloria S.
Susie
Richard
Rosie
Mary
DATE
17-X-24

FIG. 4

Figure 5

Family Mi: There is no known contact with tuberculosis. *Housing:* Five rooms for eight persons. *Cleanliness:* Fair. *Diet:* Sufficient. Ida, Mary, Minnie and Bertha are slightly overweight. *Financial status:* Fair.

Remarks: Evidence of tuberculous infection indicated by tuberculin reactions in 3 children, and one instance of tracheobronchial tuberculosis has made its appearance with increasing age of children.

Figure 6

Family Fa: There is no known contact with tuberculosis. The father died of pneumonia in 1921; he was ill only about one week. *Housing:* Five rooms and bath for eight persons. *Cleanliness:* Fair. *Diet:* Sufficient but low in proteins. *Financial status:* Poor.

Remarks: Tuberculin reactions in younger children are minimal (with 1 mgm.) and transient.

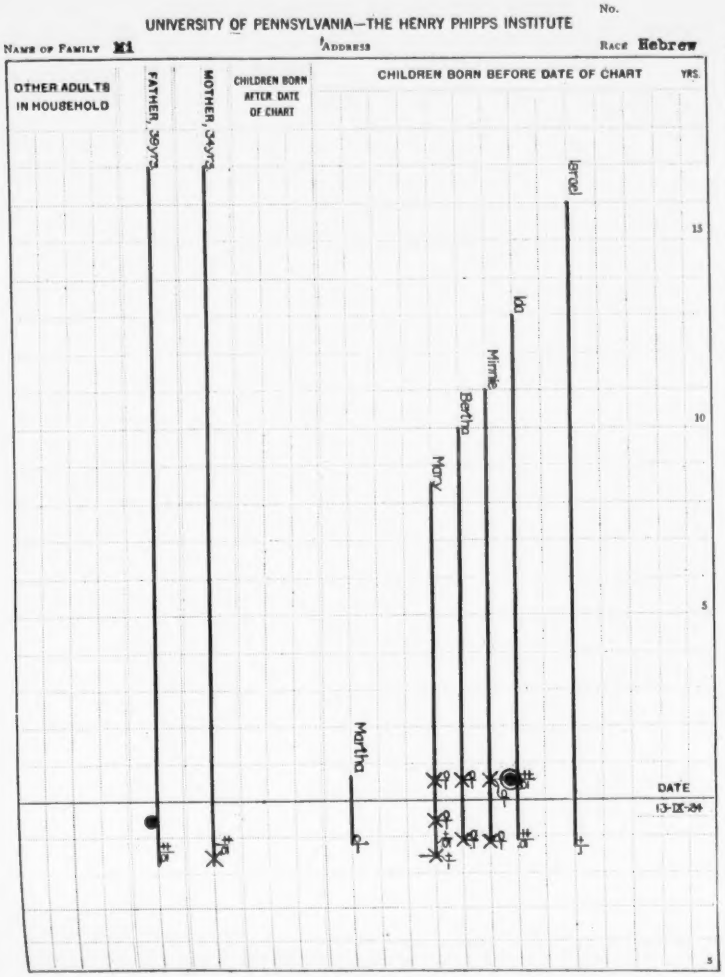

No.
UNIVERSITY OF PENNSYLVANIA—THE HENRY PHIPPS INSTITUTE
NAME OF FAMILY Mi
ADDRESS
RACE Hebrew
OTHER ADULTS IN HOUSEHOLD
FATHER, 39yrs.
MOTHER, 34yrs.
CHILDREN BORN AFTER DATE OF CHART
CHILDREN BORN BEFORE DATE OF CHART
YRS.
Israel
Leo
Minnie
Bertha
Mary
Martha
15
10
5
DATE
13-IX-24

FIG. 5

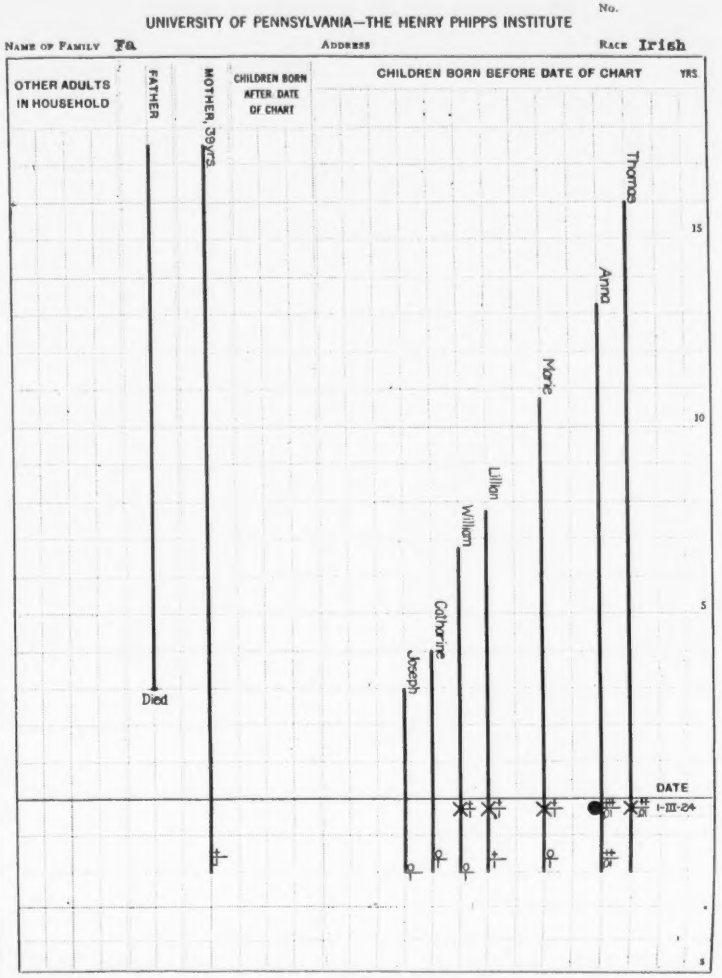

No.
UNIVERSITY OF PENNSYLVANIA—THE HENRY PHIPPS INSTITUTE
NAME OF FAMILY Fa
ADDRESS
RACE Irish
OTHER ADULTS IN HOUSEHOLD
FATHER
MOTHER, 39yrs.
CHILDREN BORN AFTER DATE OF CHART
CHILDREN BORN BEFORE DATE OF CHART
YRS.
Thomas
Anna
Marie
Lillian
William
Catherine
Joseph
Died
15
10
5
DATE
1-III-24

FIG. 6

Figures 7 and 8

Family Mf: There is no known contact with tuberculosis. The father died of influenza in 1918. He worked until one week before death and was ill only two days. The mother and grandmother are apparently well, but refuse examination. Two children died in infancy of gastrointestinal disease.

Tuberculosis of the tracheobronchial lymph nodes: Francis is well. Roentgenograms show in the left lung-field: two nodules (calcified), one 0.2 cm. across and one 0.7 x 0.5 cm., close to the chest-wall anteriorly, and two irregular opaque masses close to the bronchus to the upper lobe, one 1.1 x 0.8 cm., and one 1.3 x 1.1 cm.

Housing: Seven rooms for five persons. *Cleanliness:* Good. *Diet:* Fairly sufficient. *Financial status:* Fair.

Remarks: Though two children have demonstrable tuberculous lesions none react with tuberculin.

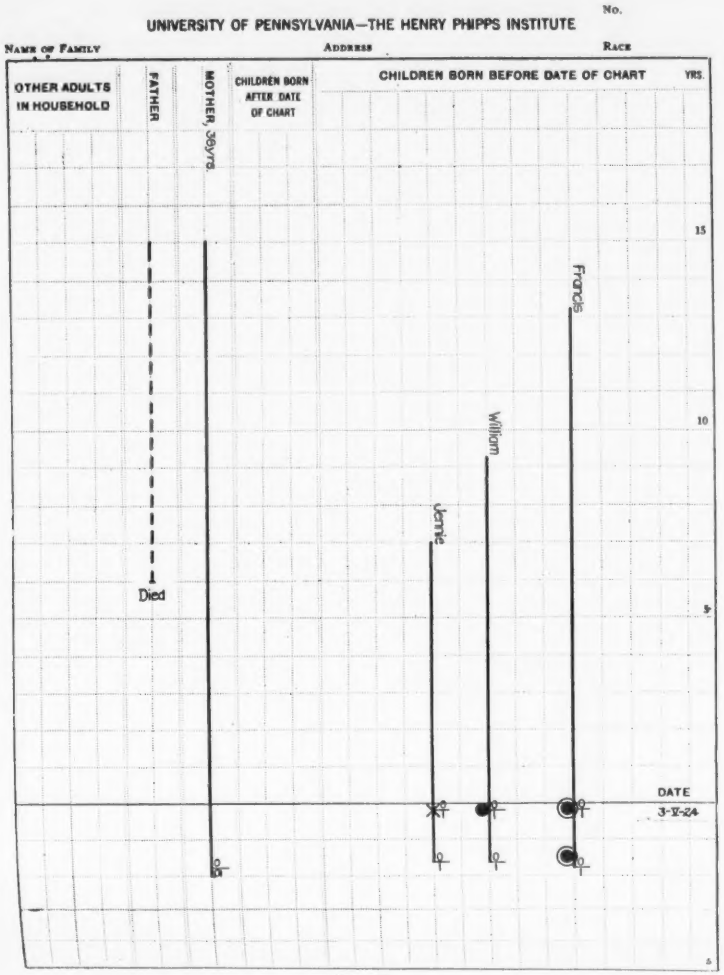
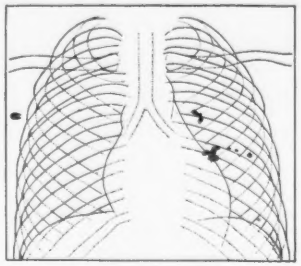
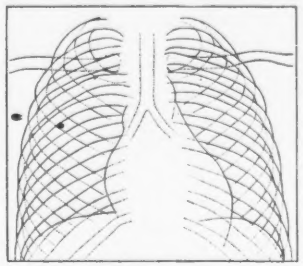


Fig. 7



Francis Mf



William Mf

Fig. 8

Figures 9 and 10

Family Ac: Probable source of contact: (1) Mother; (2) maternal aunt. *Duration of contact:* (1) Mother, seven years, ending within the period of observation. (2) Maternal aunt, four years, still continuing.

Pulmonary tuberculosis of the mother: She was first seen in September, 1921, with a history of repeated "colds" for three years. Cough and expectoration had been persistent for six months. The physical signs were those of a far-advanced lesion. Except for a period of sanatorium care the patient remained at home continuously till death in September, 1925. She was said to be careful after diagnosis in disposal of sputum.

Latent apical lesion of the father: Joseph *Ac* reports no complaints, and is very well nourished. Temperature and pulse are normal. Roentgenograms of February, 1925 and 1926, show moderately dense infiltration of the right apex and slighter infiltration of the left apex.

Pulmonary tuberculosis and tuberculosis of tracheobronchial lymph nodes of the maternal aunt: Celia M., in February, 1922, complained of slight cough with scant white expectoration. Between 1922 and the present the sputum was negative except in May, 1925, when it contained a few acid-fast microörganisms. Suspicious physical signs had been found at times at the apex, but no apical râles. The sputum has been occasionally streaked with blood. The patient had gained 20 pounds in February, 1926. Temperature and pulse were always normal. Roentgenograms of February, 1925, show a granular mass (calcified), 1.4 x 0.8 cm., at the left bronchial bifurcation, and a nodule 0.5 cm. peripherally in the lung. There is moderately dense infiltration of the left apex and a slight infiltration of the right apex. Roentgenograms of February, 1926, show no definite change.

Pulmonary tuberculosis and tuberculosis of tracheobronchial lymph nodes in a sister: Anna was first seen November, 1923, aged 12 years. Roentgenograms showed a sharply defined nodule (calcified) near the base of the right lung and three granular masses, one in the hilum of the right lung, one at the bifurcation of the trachea and one to the right of the trachea, measuring 1.0 x 0.6 cm., 1.7 x 1.2 cm., and 1.0 x 0.8 cm., respectively. These observations were confirmed and widespread infiltration of the left apex was found in March, 1926. Râles were heard at this time over the left apex posteriorly. There is slight morning cough occasionally with scant sputum; temperature and pulse are normal.

Tuberculosis of tracheobronchial lymph nodes in a sister: Rose was first seen November 1923, aged 11 years. Physical signs were negative. Roentgenograms showed granular masses (calcified), one in the right hilum, 0.6 x 0.3 cm.; and one below the carina, 1.7 x 0.8 cm. These were confirmed, March, 1926. Physical signs have always been negative. In April, 1926, she complained of fatigue, but was well nourished and without cough. Temperature and pulse were within normal limits.

Housing: Four rooms and bath for five persons. *Diet:* Sufficient. *Cleanliness:* Good. *Financial status:* Fair.

FIG. 9

FIG. 10

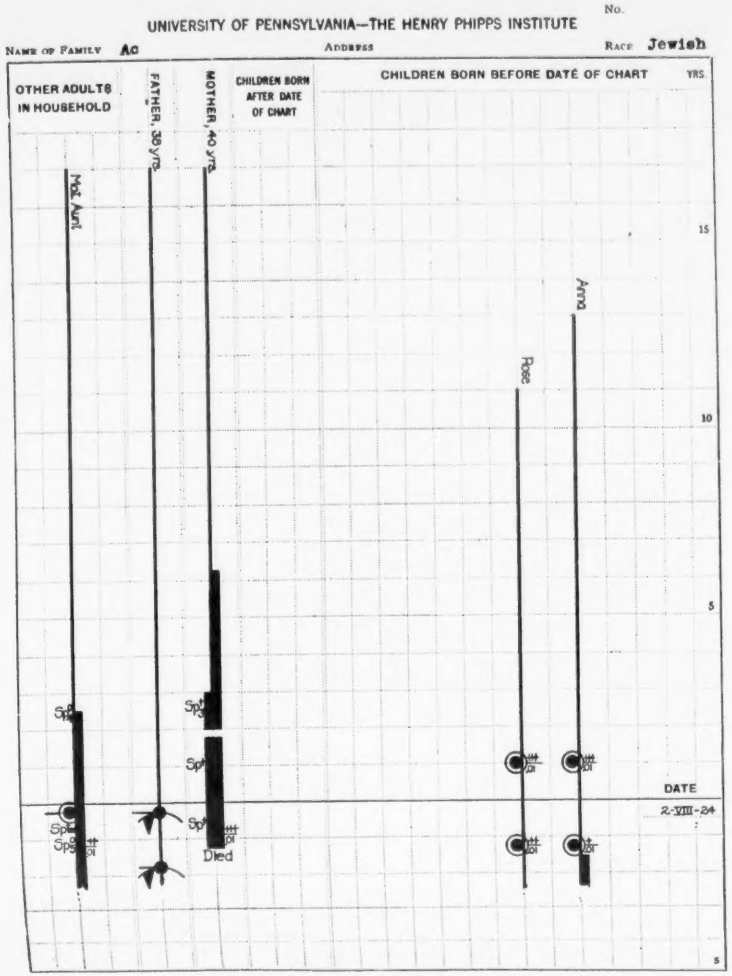
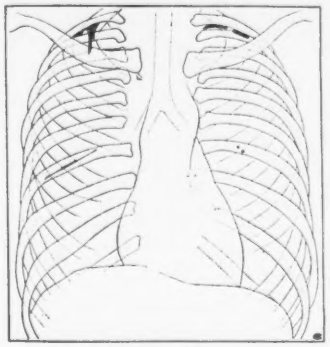
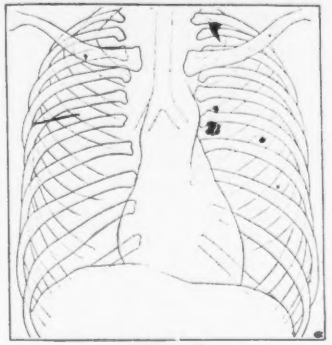


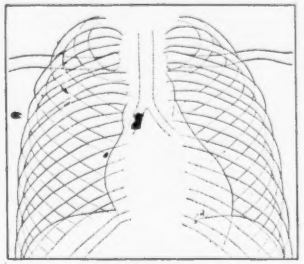
Fig. 9



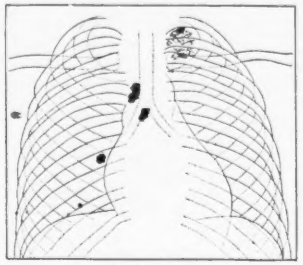
Joseph Ac



Celia M.



Rose Ac



Anna Ac

Fig. 10

Figures 11 and 12

Family Bc: Probable source of infection: Father. *Duration of contact:* $2\frac{6}{12}$ years, ending within the period of our observation.

Pulmonary tuberculosis of the father: On his first visit, January, 1923, he gave a history of cough for two years, with expectoration for two weeks. Physical signs were those of a moderately advanced lesion with unfavorable outlook. Except for two hospital admissions this patient was at home until his death. It is said he was careful in sputum disposal after diagnosis.

Latent apical tuberculosis of the mother: She was examined as a contact though she gave no complaints. When first seen February, 1925, roentgenograms showed infiltration of the right and left apices. In February, 1926, the bilateral infiltrations were found slightly more extensive by roentgenogram. Physical examination was negative, and the patient complained of no discomfort.

Tuberculosis of tracheobronchial lymph nodes: Roentgeonograms of Josephine, of February, 1925, show a nodule in the peripheral part of the left lung. In February, 1926, there is, in addition, a granular mass, 1.3 x 0.6 cm., above the left bronchus.

Housing: Three rooms for eleven persons. *Cleanliness:* Excellent. *Diet:* Sufficient. *Financial status:* Poor.

Note: In fig. 12 family is incorrectly designated "*Ba*" instead of *Bc*.

Fig. 11

Fig. 12

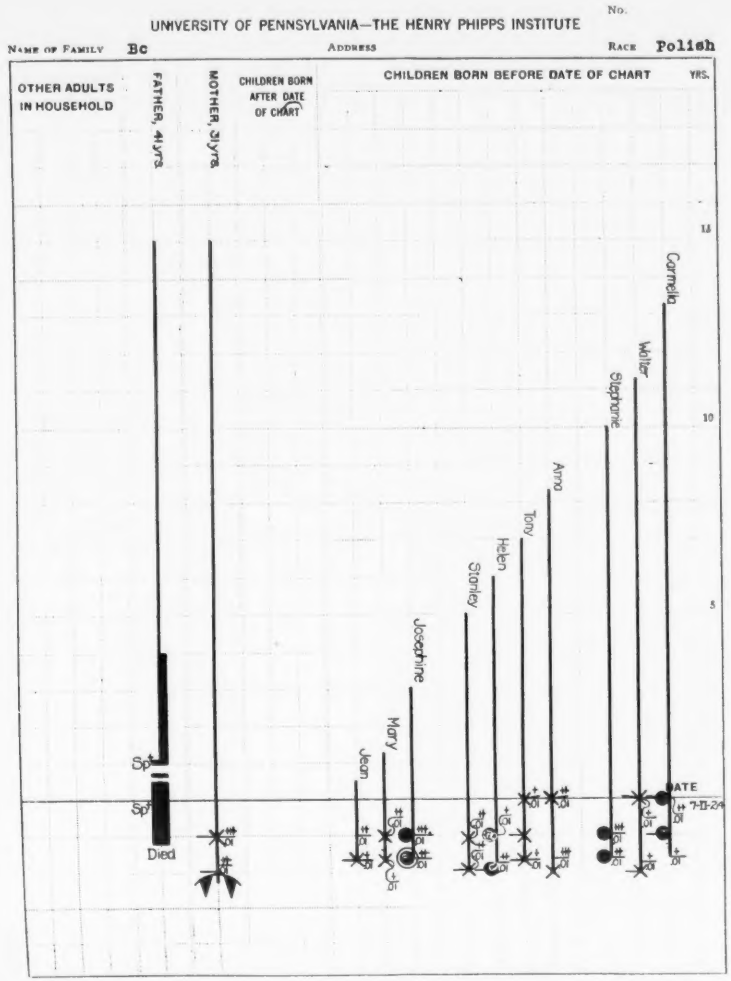
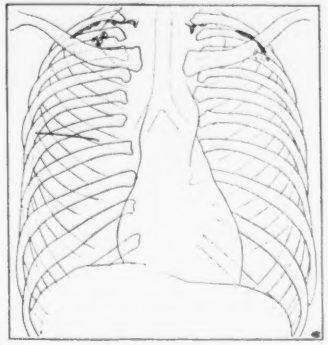
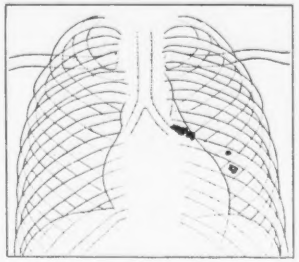


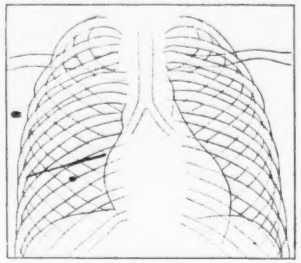
FIG. 11



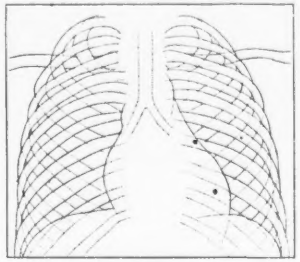
Annie Ba (Mother)



Josephine Ba



Helen Ba



Stephanie Ba

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FIG. 12

Figures 13 and 14

Family Ca: Probable source of infection: (1) Mother; (2) maternal uncle. *Duration of contact:* (1) Mother, 4 years, ending 13 months prior to the period of observation of the children. (2) Maternal uncle, 13 months, ending at the beginning of the period of observation.

Pulmonary tuberculosis of the mother: She was ill for three years prior to diagnosis in 1921. Her condition became rapidly worse, and she died in August, 1922. She was not careful in sputum disposal until shortly before death.

Pulmonary tuberculosis of the maternal uncle: He was far advanced, with unfavorable outlook when first seen, September, 1923. He dated his illness only one year prior to diagnosis, but in view of the lesion it was probably longer. He was admitted to the hospital in October, and died there, January, 1924. He was not careful in sputum disposal prior to September, 1923.

Tuberculosis of tracheobronchial lymph nodes of children: (1) Edward was apparently well. Roentgenograms show a dense granular mass, 1.5 x 1.1 cm., at the main division of the right bronchus. (2) Beatrice was also well. Roentgenograms show a dense granular mass, 2.5 x 1.3 cm., overlying the right bronchus at its origin from the trachea. (3) Elwood was well. Roentgenograms showed dense spots, 0.6 x 0.4 and 0.5 x 0.3 cm., respectively, close to the lower lobe branch of the left bronchus, and a dense mass, 0.9 x 0.6 cm., close to the origin of the left bronchus. (4) Robert was also well, and roentgenograms show in the anterior part of the right lung a group of five sharply defined nodules, each about 2 mm. across, and close to the right bronchus a dense mass, 1.6 x 1.0 cm., and another 1.1 x 0.6 cm. These children were well cared for and looked healthy, except Beatrice who was rather thin, pale and listless. The two youngest children slept with the mother until February, 1922.

Housing: Seven rooms and bath for seven persons. *Cleanliness:* Good. *Diet:* Insufficient until 1923; thence adequate. *Financial status:* Fair.

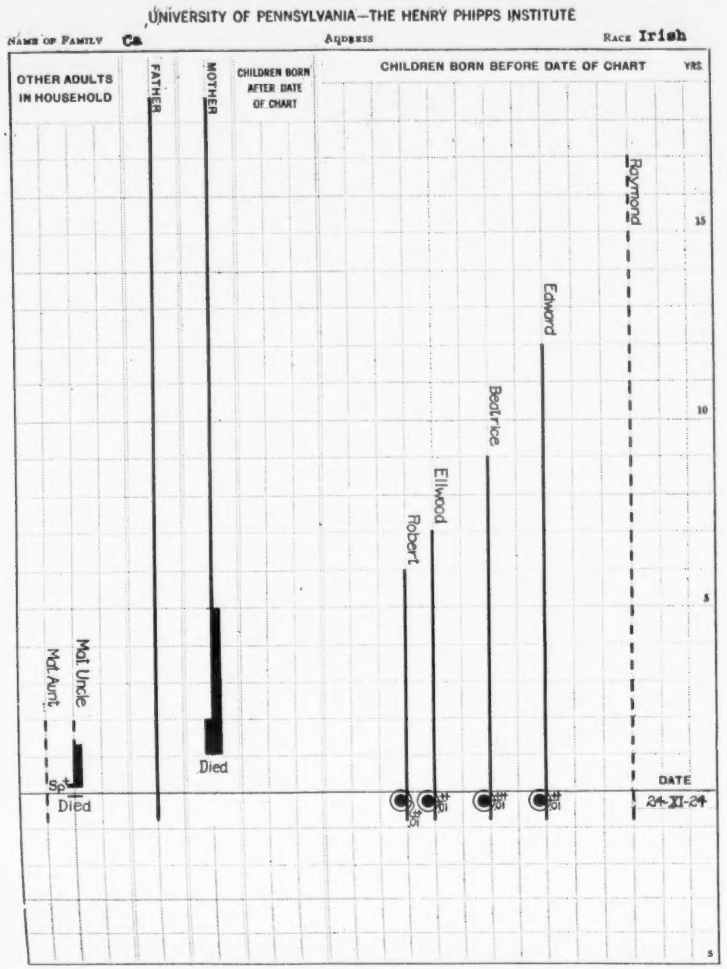

UNIVERSITY OF PENNSYLVANIA—THE HENRY PHIPPS INSTITUTE
NAME OF FAMILY Ca
ADDRESS
RACE Irish
OTHER ADULTS IN HOUSEHOLD
FATHER
MOTHER
CHILDREN BORN AFTER DATE OF CHART
CHILDREN BORN BEFORE DATE OF CHART
YRS.
Raymond
Edward
Beatrice
Elwood
Robert
15
10
5
5
Mat Uncle
Mat Aunt
Died
Died
DATE
24-XI-24

FIG. 13

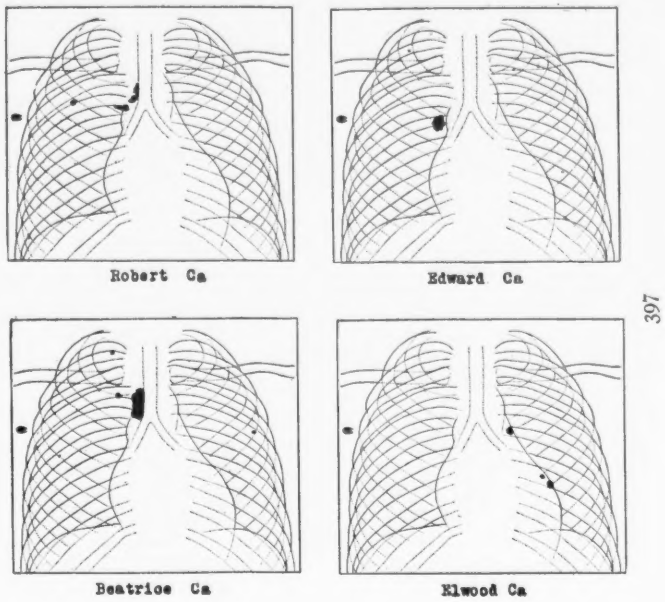

Robert Ca
Edward Ca
Beatrice Ca
Elwood Ca

FIG. 14

Figures 15 and 16

Family Dh: Probable source of infection: Father. *Duration of contact:* 5 years, possibly 6 and 6/12 years, ending prior to the period of observation.

Pulmonary tuberculosis of the father: He was ill during five to six years prior to the diagnosis in June, 1923, of far-advanced tuberculosis, with sputum positive. He was at home until his death in August, 1923.

Latent apical tuberculosis of the mother: Mrs. Bessie *Dh* has had no symptoms. Physical examination is negative. Roentgenograms of March, 1926, show bilateral, moderately dense infiltrations, appearing as irregular networks as low as the anterior level of the fourth rib on the right and the fifth on the left.

Tuberculosis of the tracheobronchial lymph nodes of a brother: Charlie has no complaints. Roentgenograms show two dense granular masses, 1.3 x 0.7 cm. and 1.6 x 0.6 cm., close to the left bronchus.

Housing: Six rooms for seven persons. *Cleanliness:* Fair. *Diet:* Probably sufficient. *Financial status:* Fair.

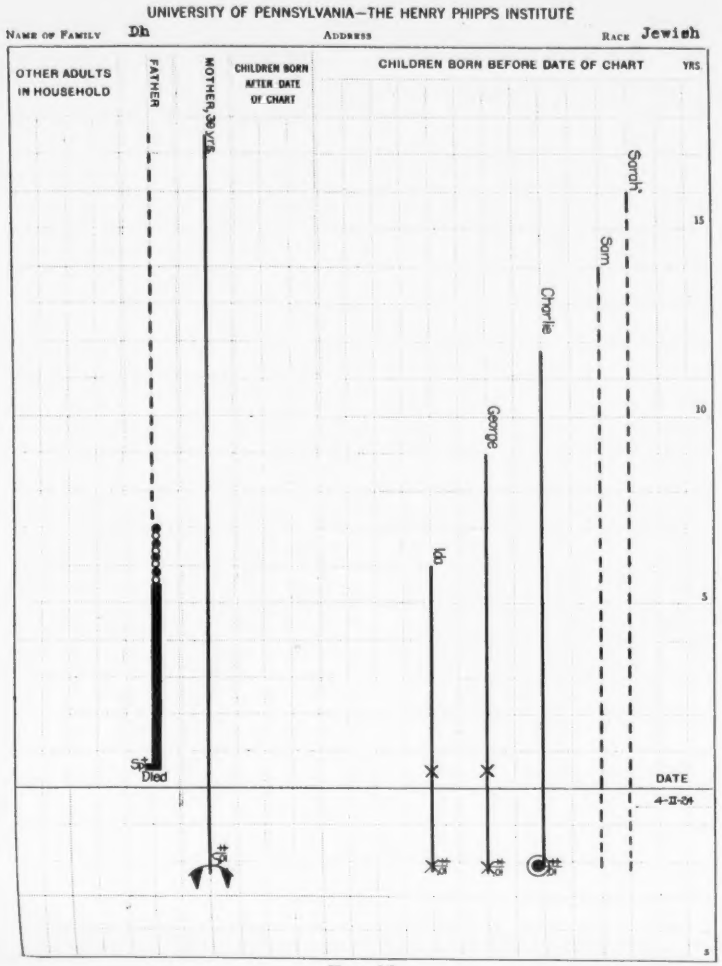
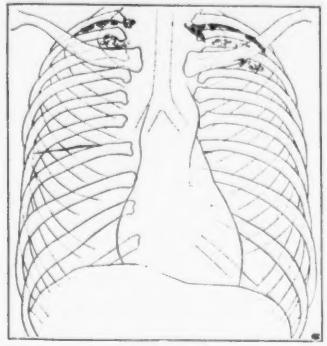
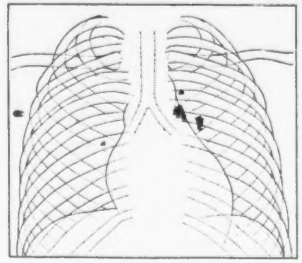


FIG. 15



Bessie Dh



Charles Dh

FIG. 16

Figures 17 and 18

Family Ka: Probable source of infection: Father (and two sisters, see below). *Duration of contact:* About 2 and 6/12 years, ending 1914.

Pulmonary tuberculosis of the father: He died of pulmonary tuberculosis early in 1914. He is said to have been careless in disposal of sputum.

Pulmonary tuberculosis of an uncle: He was not a patient of the dispensary of the Henry Phipps Institute. He was ill one month prior to admission to hospital, where he died, February, 1919. It is doubtful if he was careful in disposal of sputum.

Pulmonary tuberculosis and tuberculosis of tracheobronchial lymph nodes in sisters: (1) Margaret in August, 1917, came to the dispensary with a history of cough and expectoration during several weeks. Medium crackling râles were heard over the front and back on the right, and over the left upper third. She was able to resume work at the end of 1918, and has since married. Roentgenograms of November, 1925, show a right apical scar-like infiltration. In the left lung there is a sharply defined nodule (calcified) anteriorly, and sharply defined, granular masses, one, 1.3 x 0.7 cm., near the left bronchus and one, 1.8 x 1.7 cm., at the carina. This patient is free from symptoms. It is doubtful if she has been careful in disposal of sputum. (2) Katherine in January, 1918, was said to have had a slight cough irregularly for 3 and one-half years. Râles were heard on the right front and back and in the lower half on the left side. The physical signs were little changed in March, 1924. Roentgenograms of March, 1924, and February, 1925, show, on the right, patches of irregular noded network in the upper two-thirds and irregular strands in the lower third; at the posterior level of the fifth interspace outside the midthoracic line, sharply defined nodules (calcified), each about 2 mm. across, forming a group 3 cm. across; beside the main-stem bronchus, two granular, dense, sharply defined masses, 1.1 x 0.5 cm. and 0.6 x 0.6 cm., respectively; another similar mass, 1.3 x 0.6 cm., to the right of the trachea: these last three representing calcification in lymph nodes. On the left, irregular strands are to be seen in the apex and the middle third, less dense than on the right; and two dense granular masses are seen on the main bronchus, one, 1.0 x 0.7 cm., one, 0.5 x 0.4 cm. *Helen (Ka) C:* She is apparently well. Roentgenograms show a nodule with a scar-like strand at the right apex. Two nodules (calcified) are found in the left lung field.

Housing: Four rooms for six persons. *Cleanliness:* Fair. *Diet:* Probably sufficient, but low in proteins. Financial status: Poor.

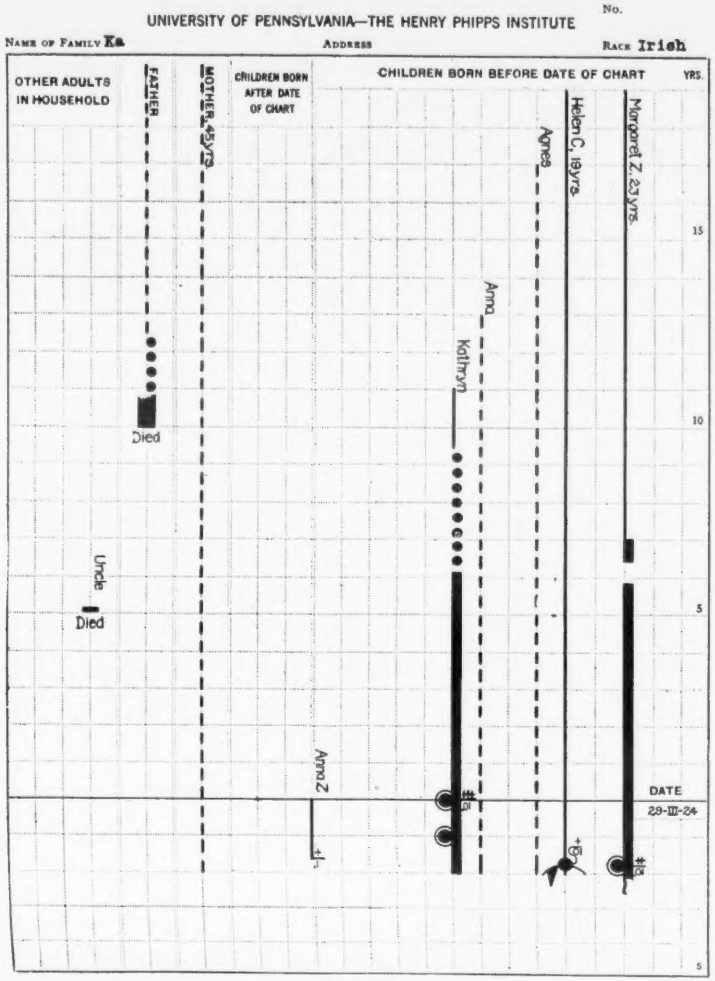
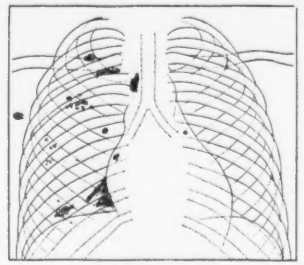
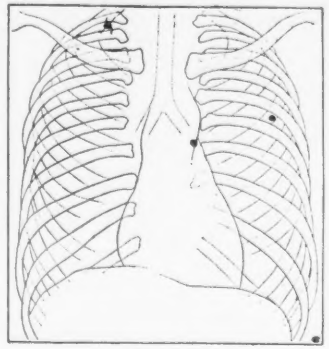


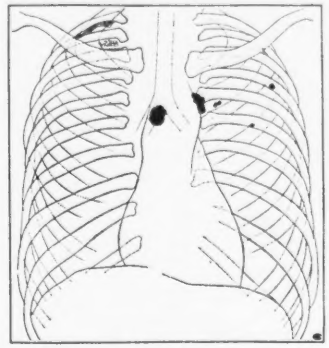
FIG. 17



Katherine Ka



Helen (Ka)C



Margaret (Ka)Z

FIG. 18

Figures 19 and 20

Family Ia: Probable source of infection: Father. *Duration of contact:* 8 and one-half years, ending prior to the period of our observation.

Pulmonary tuberculosis of the father: He first came to the dispensary in March, 1915, with the history of cough present irregularly. Physical signs were those of a moderately advanced lesion. He remained at home, refusing sanatorium care, and died July, 1923. He is said to have been careful in disposal of sputum.

Latent apical tuberculosis of the mother: Mrs. Susie Ia has no complaints. Physical examination is negative. Roentgenograms of March, 1926, show apical scar-like infiltration of each apex, with salients directed into the lung.

Pulmonary tuberculosis of brother: Micail, in April, 1923, was ill two months prior to the diagnosis of pulmonary tuberculosis, which was moderately advanced with sputum positive. He was in a hospital from October until his death in March, 1924.

Tuberculosis of the lung and of tracheobronchial lymph nodes of sister: Jennie was first seen in February, 1924, when she was apparently well and 7 pounds overweight. Roentgenograms showed a sharply defined nodule near the base of the right lung and a coarsely granular mass near the bronchus to the lower lobe, 1.9 x 0.4 cm. She did not return to the dispensary, but was reported apparently well until October, 1925, when she became suddenly ill with respiratory symptoms and positive sputum. She was in hospital about 3 weeks, and died at home January, 1926.

Latent apical tuberculosis of the paternal grandmother: Mrs. Mary Ia has lived with this family since September, 1925. She is apparently well. Roentgenograms of January, 1926, show conspicuous scar-like infiltration of each apex to the anterior level of the second rib. Physical examination is negative. Her son who lived with her before she joined this household died in February, 1925, of pulmonary tuberculosis (with tubercle bacilli in sputum).

Housing: Two rooms for five persons. *Cleanliness:* Fair. *Diet:* Fairly sufficient. *Financial status:* Poor.

FIG. 19

FIG. 20

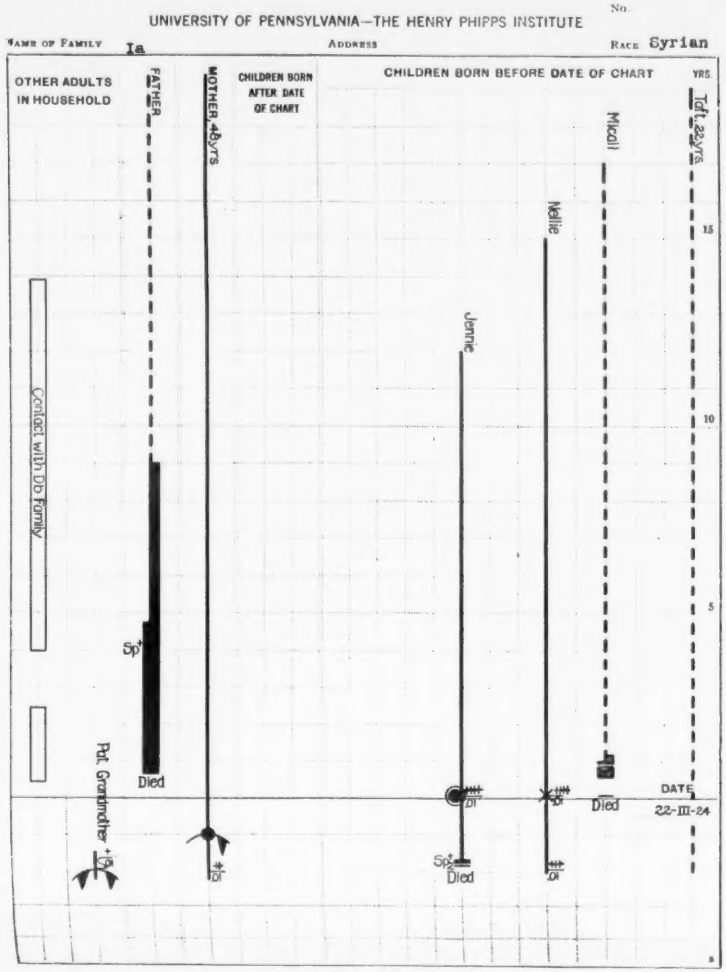
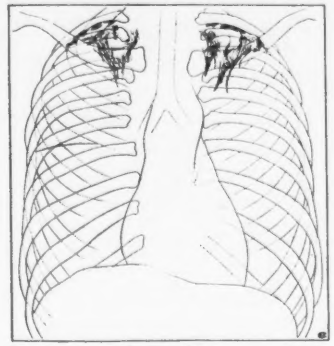
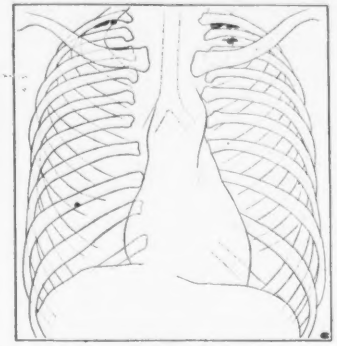


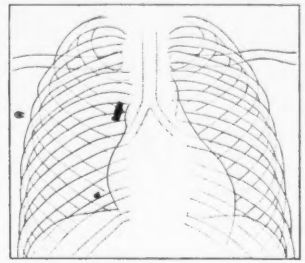
Fig. 19



Mary Ia



Sussie Ia



Jennie Ia

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Fig. 20

FIG. 21

FIG. 22

Figures 21 and 22

Family Db: Probable source of infection: Mother. *Duration of contact:* Over 12 and one-half years to February, 1926; still continuing. The family has been in intimate contact with Family *Ia*, Mrs. *Db* being the sister of Mr. Cain *Ia* (see fig. 19).

Pulmonary tuberculosis of the mother: When Mrs. Carrie *Db* first visited the dispensary in July, 1913, physical signs were those of a moderately advanced lesion. Roentgenograms of December, 1924, and March, 1926, show an irregular noded network throughout the upper three-fourths of the right and left lung-fields. She is not careful in disposal of sputum.

Latent apical tuberculosis of the father: Roentgenograms of October, 1925, show on the right a diffuse strand-like infiltration of the apex, and on the left dense infiltration above the clavicle probably with cavity.

Tuberculous osteomyelitis of foot of brother: Sesson has been under the care of the Pennsylvania Hospital from February, 1915, to March, 1918, and January to May, 1919.

Housing: Three rooms for six persons. *Cleanliness:* Poor. *Diet:* Insufficient. All children are undernourished. *Financial status:* Poor.

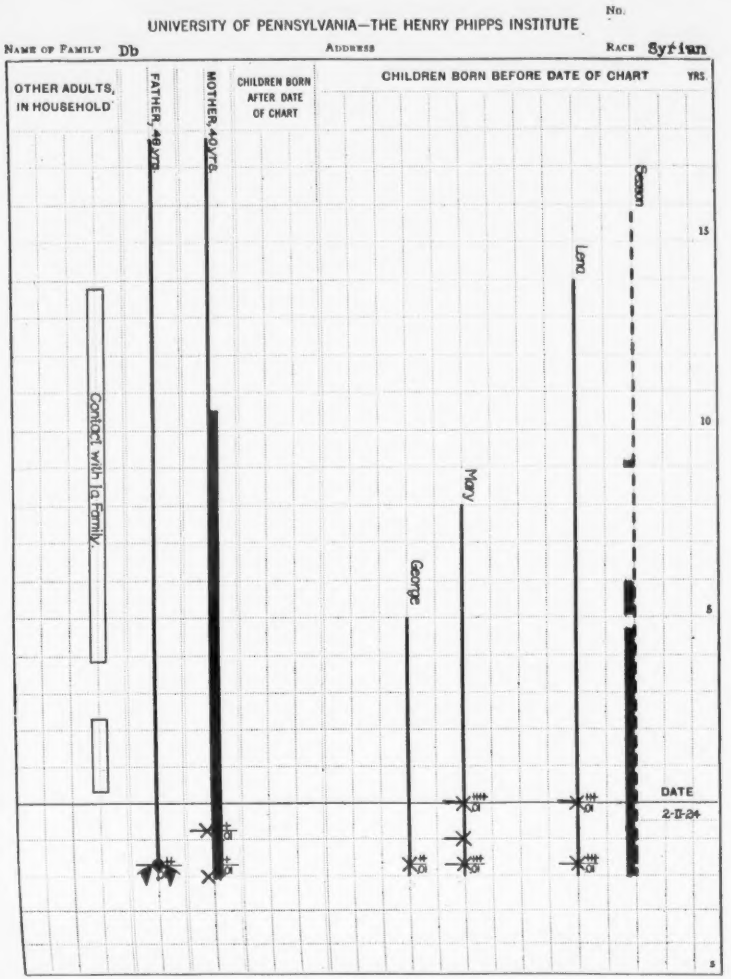
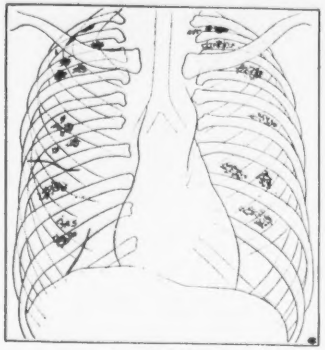
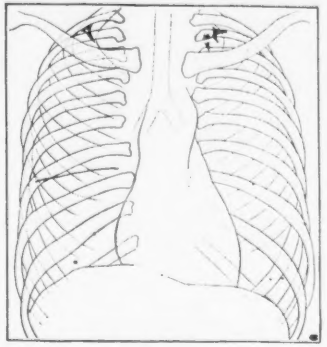


FIG. 21



Carrie Db



Cain Db

FIG. 22

Figures 23, 24 and 25

Family Mh: Probable source of infection: (1) Mother; (2) father. *Duration of contact:* (1) Said to be 2 and 5/12 years to May, 1926, but probably much longer; (2) 7 and 5/12 years to May, 1926, perhaps less.

Pulmonary tuberculosis of the father: Mr. John *Mh* was first seen June, 1923, with a history of susceptibility to colds for five years, loss of weight during the past year, and severe morning cough during the past seven weeks. Physical signs were those of a minimal lesion. Roentgenograms of March, 1925, show right and left apical scar-like infiltrations and a nodule (calcified in the left lung). This patient is not careful in disposal of sputum.

Pulmonary tuberculosis of the mother: Mrs. Sallie *Mh* was first seen July, 1923, with a history of cough of six weeks' duration. The indifference of this patient, together with the evidences of the lesion, make it likely that the illness with cough has been much longer. Physical signs were those of a moderately advanced lesion. Roentgenograms of February, 1925, show strand-like infiltration throughout the right lung and mottling in the left upper third. Râles are present over the right upper two-thirds. This patient is exceedingly careless in disposal of sputum.

Tuberculosis of the lymph nodes and of lung of brother and sister: (1) John, Jr., first seen December, 1923, was thin, but otherwise well. A few fine râles were heard above the clavicle on the right on only one occasion. Roentgenograms of December, 1923, show two sharply defined nodules (calcified) peripherally in the left lung-field, mass 1.5 x 1.5 cm. close to the left main bronchus, and a soft, cloudy infiltration in the right apex. He did not report again until February, 1926, when râles were present over the right upper half. Roentgenograms showed on the right a soft thick-set mottling in the upper half; and on the left, similar mottling, together with rarefied areas up to 3 cm. across, interpreted as cavities. At this time, he had had cough for seven weeks and looked ill. (2) Anna was first seen, December, 1923. She gave no complaints and was well nourished. Medium coarse râles were present over the right upper half. Roentgenograms showed a sharply defined nodule (calcified) in the right lung-field peripherally and a soft mottling in the right upper half and left upper third. In March, 1925, a granular mass (calcified), 1.5 x 0.8 cm., was seen to the right of the trachea. In February, 1926, in oblique exposures not made hitherto, two additional granular masses (calcified) were noted, one 2.0 x 1.12 cm. on the right bronchus at its origin, one 1.1 x 0.6 cm. below the carina. The child reported that she had no cough and said she felt well. She was thin.

Tuberculosis of the tracheobronchial lymph nodes of sister: Florence was first seen February, 1926. Physical signs were negative. Roentgenograms showed in the right costophrenic sulcus a soft granular mass (calcified), 2.6 x 1.2 cm., and on the right bronchus a similar mass, 1.0 x 0.8 cm.; at the carina another, 1.5 x 1.3 cm., and to the right of the trachea one 2.3 x 1.5 cm.

Housing: Five rooms and bath for eight persons. *Cleanliness:* Good. *Diet:* Probably sufficient. *Financial status:* Poor.

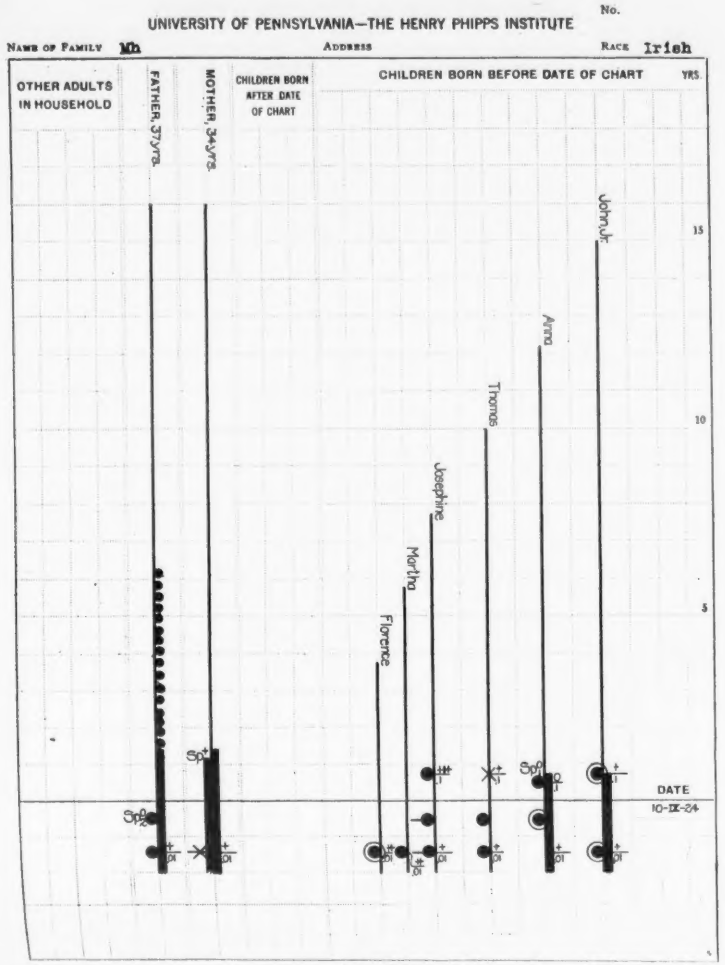

No.
UNIVERSITY OF PENNSYLVANIA—THE HENRY PHIPPS INSTITUTE
NAME OF FAMILY Mh
ADDRESS
RACE Irish
OTHER ADULTS IN HOUSEHOLD
FATHER, 37 yrs.
MOTHER, 34 yrs.
CHILDREN BORN AFTER DATE OF CHART
CHILDREN BORN BEFORE DATE OF CHART
YRS.
John Jr.
Anna
Thomas
Josephine
Martha
Florence
15
10
5
DATE
10-IX-24

Fig. 23

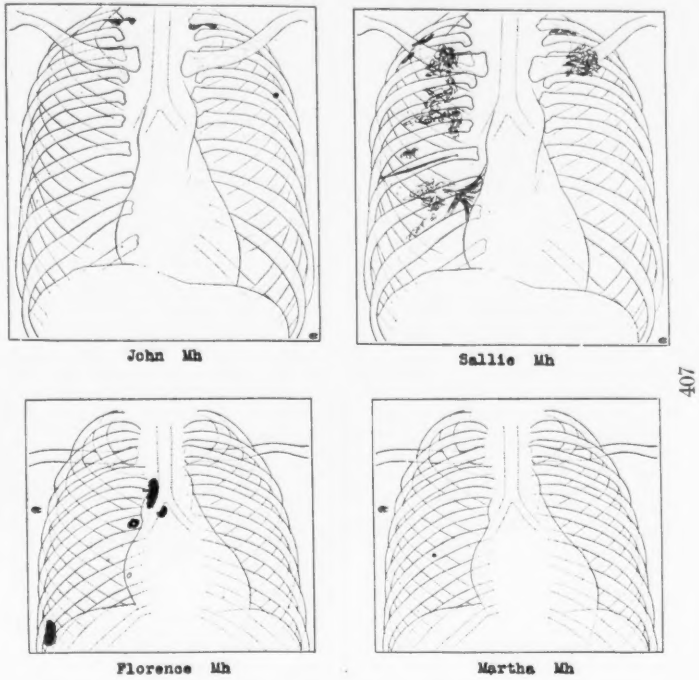

John Mh
Sallie Mh
Florence Mh
Martha Mh

Fig. 24

Figure 25

See page 406

Figure 26

Family Va: Source of infection: Father. *Duration of contact:* 4 and 6/12 years.

Pulmonary tuberculosis of the father: He was ill four years to diagnosis in November, 1922, of far-advanced pulmonary tuberculosis. He was probably careful in disposal of sputum after diagnosis.

Pulmonary tuberculosis of the lung and tuberculosis of tracheobronchial lymph nodes of a child: Josephine in June, 1924, had grouped medium coarse râles in the right upper half on two examinations at intervals of 9 days, but subsequent physical examinations have been negative. Roentgenograms showed interlacing strands and a few spots on the right side, chiefly in the region of the middle lobe, and three sharply defined, irregular, granular masses, 0.6 x 0.6 cm., 0.8 x 0.5 cm. and 2.1 x 1.2 cm., close to the right bronchus.

Tuberculosis of other children: One child died, aged one year, of pneumonia and meningitis, presumably tuberculous, and another March, 1924, aged 7/12 years, of pulmonary tuberculosis. One child died March, 1922, aged 1 and 6/12 years, of a gastrointestinal disorder.

Pulmonary tuberculosis of a maternal uncle: He was ill for 15 years prior to his death, apparently from pulmonary tuberculosis. He lived in the same household with family *Va* as indicated on chart.

Housing: Four rooms and bath for five persons, varied owing to intermittent mingling of this family with that of the maternal uncle. *Cleanliness:* Fair. *Diet:* Sufficient. *Financial status:* Poor.

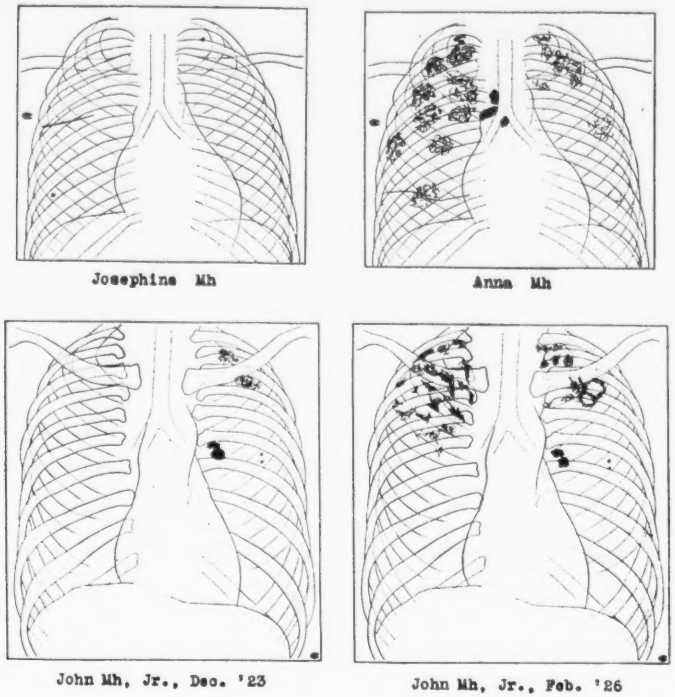

Josephine Mh
Anna Mh
John Mh, Jr., Dec. '23
John Mh, Jr., Feb. '26

FIG. 25

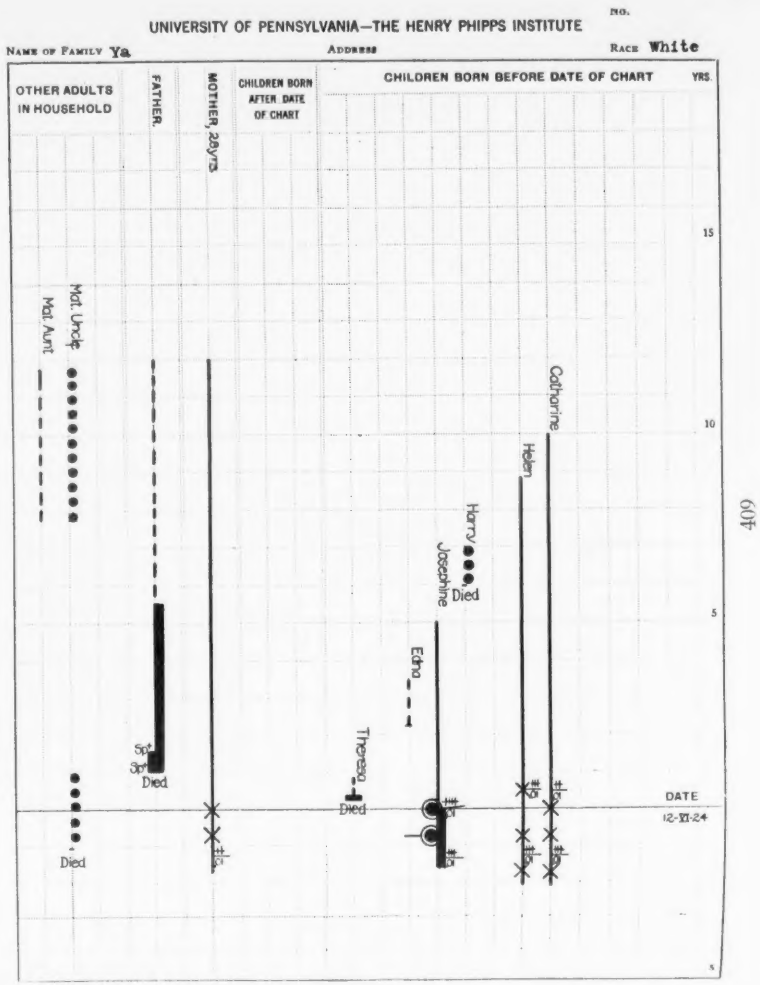

UNIVERSITY OF PENNSYLVANIA—THE HENRY PHIPPS INSTITUTE
NO.
NAME OF FAMILY Ya
ADDRESS
RACE White
OTHER ADULTS IN HOUSEHOLD
FATHER.
MOTHER, 28yrs
CHILDREN BORN AFTER DATE OF CHART
CHILDREN BORN BEFORE DATE OF CHART
YRS.
15
10
5
Mat. Aunt
Mat. Uncle
Died
5p
3p
Died
Theresa
Died
Edna
Josephine
Harry
Died
Helen
Catharine
DATE
12-XI-24

FIG. 26

Figures 27 and 28

Family Zc: Source of infection: Father. *Duration of contact:* 4 and 6/12 years, ceasing within the period of our observation.

Pulmonary tuberculosis of the father: He was first seen, June, 1920, with far-advanced pulmonary tuberculosis and tuberculous laryngitis. He was careless in disposal of his sputum.

Latent apical tuberculosis of sister: Mary had no symptoms, and her weight was normal. Roentgenograms showed a left apical infiltration. She has married recently and is apparently well.

Tuberculosis of tracheobronchial lymph nodes: (1) Roentgenograms of William in January, 1926, show a sharply defined nodule (calcified) in the right lung anteriorly and three granular masses (calcified), one 1.8 x 0.8 cm. close to the right bronchus, one 2.1 x 1.3 cm. at the carina, and one 2.1 x 0.7 cm. to the right of the trachea. He was free from symptoms and his weight was normal. (2) Helen's roentgenograms of January, 1926, show four granular masses (calcified), one on the right bronchus 0.7 x 0.5 cm., one on the left bronchus 0.6 x 0.4 cm., one near the carina 1.2 x 0.7 cm., and one to the right of the trachea 1.8 x 0.6 cm. There is a soft shadow in the left base. She had no symptoms.

Housing: Two rooms for seven persons. *Cleanliness:* Poor. *Diet:* Poor in protein, mostly starches. *Financial status:* Poor.

FIG. 27

FIG. 28

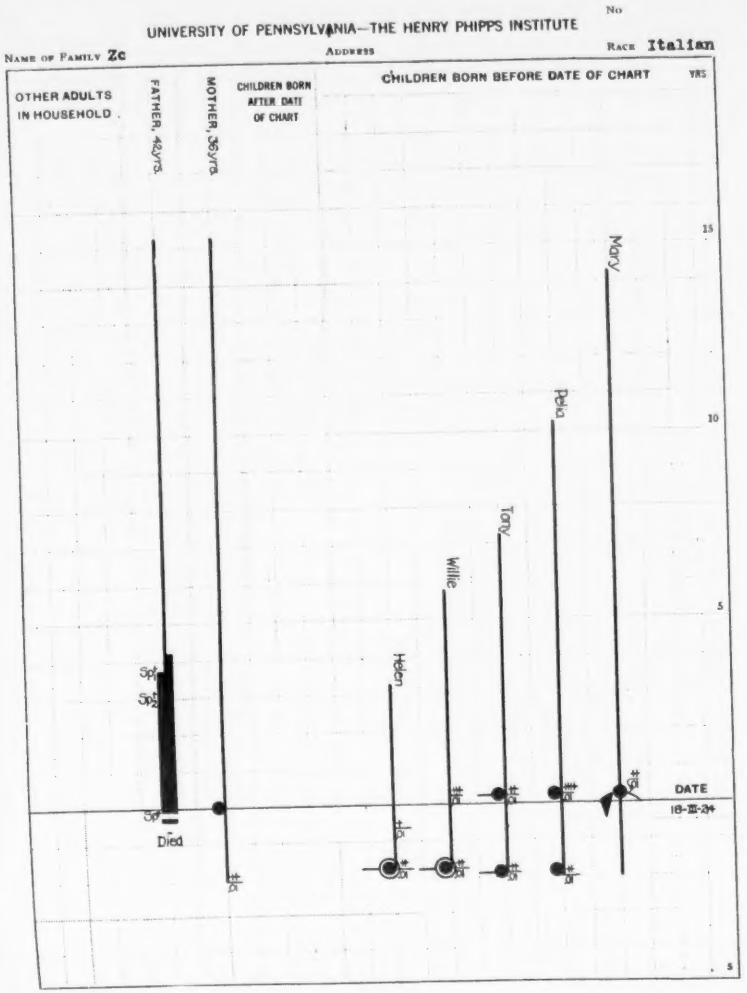

No
UNIVERSITY OF PENNSYLVANIA—THE HENRY PHIPPS INSTITUTE
Name of Family Zc
Address
Race Italian
OTHER ADULTS IN HOUSEHOLD.
FATHER, 42 yrs.
MOTHER, 36 yrs.
CHILDREN BORN AFTER DATE OF CHART
CHILDREN BORN BEFORE DATE OF CHART
YRS
15
10
5
5
Mary
Pelia
Tony
Willie
Helen
Sophie
Died
DATE
18-II-24

FIG. 27

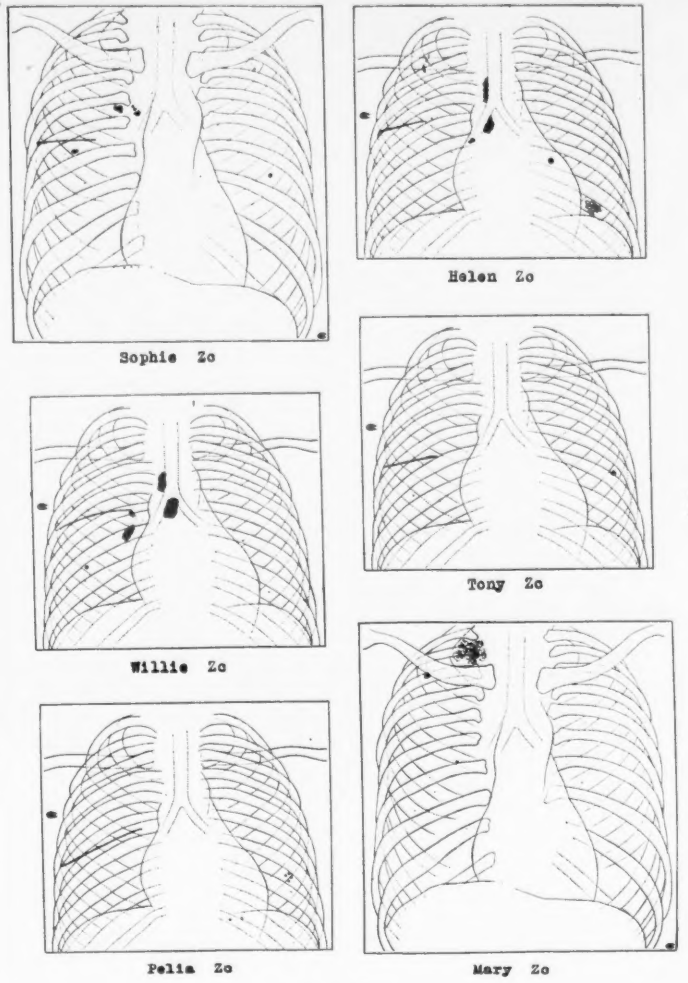

Sophie Zc
Helen Zc
Willie Zc
Tony Zc
Pelia Zc
Mary Zc

FIG. 28

Figures 29 and 30

Family Sc: Source of infection: (1) Father; (2) paternal uncle. *Duration of contact:* (1) 9 and 11/12 years, ending within the period of our observation. (2) At least 3/12 year, probably about 6 years, ending January 1922.

Pulmonary tuberculosis of the father: He was ill for eight years prior to diagnosis in February, 1924, of moderately advanced pulmonary tuberculosis with laryngitis. He was not careful in disposal of his sputum after diagnosis.

Pulmonary tuberculosis of the paternal uncle: The onset was uncertain. In October, 1921, physical signs were those of a far-advanced lesion with laryngitis. He died in this household, January, 1922. He was not careful in disposal of sputum after diagnosis.

Latent apical tuberculosis of children: (1) Anna is underweight but has no symptoms. Roentgenograms of March, 1924, show a faint cloudy left apical infiltration. Roentgenograms of February, 1926, show a definite advance of the left apical lesion, salients and strands extending to the fourth rib posteriorly, and on the right an equally advanced lesion. Physical signs are negative. This child and the two following have been sent to a sanatorium, June, 1926. (2) Rose is apparently well. Roentgenograms of April, 1926, show on the right a definite apical lesion with salients directed into the lung.

Tuberculosis of the tracheobronchial lymph nodes of a brother: Anthony is underweight. Roentgenograms of March, 1924, show a sharply defined nodule (calcified) in the tenth right interspace, and granular masses (calcified) on the main-stem bronchus, 1.0 x 0.9 and 1.2 x 0.6 cm., respectively. In February, 1926, in an oblique exposure a similar granular mass, 2.8 x 1.3 cm., is seen beside the trachea.

Housing: Eight rooms and bath for seven persons. *Cleanliness:* Good. *Diet:* Insufficient. *Financial status:* Poor.

Fig. 29

Fig. 30

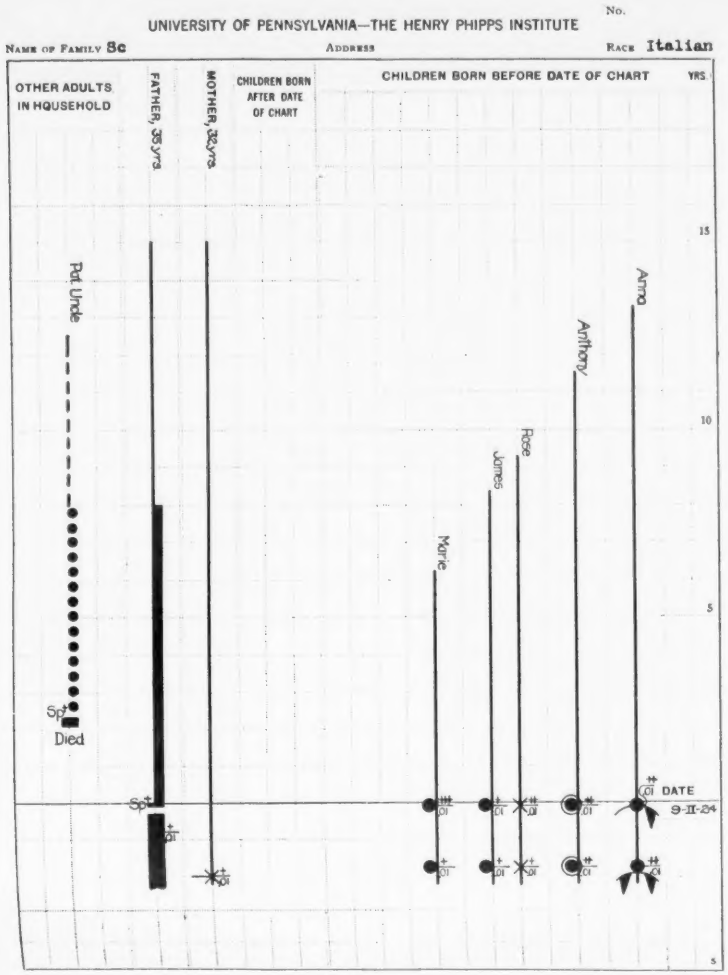

No.
UNIVERSITY OF PENNSYLVANIA—THE HENRY PHIPPS INSTITUTE
NAME OF FAMILY Sc
ADDRESS
RACE Italian
OTHER ADULTS IN HOUSEHOLD
FATHER, 35yrs.
MOTHER, 32yrs.
CHILDREN BORN AFTER DATE OF CHART
CHILDREN BORN BEFORE DATE OF CHART
YRS.
15
10
5
5
Pat Uncle
Sp
Died
Marie
James
Rose
Anthony
Anna
DATE
9-II-24

FIG. 29

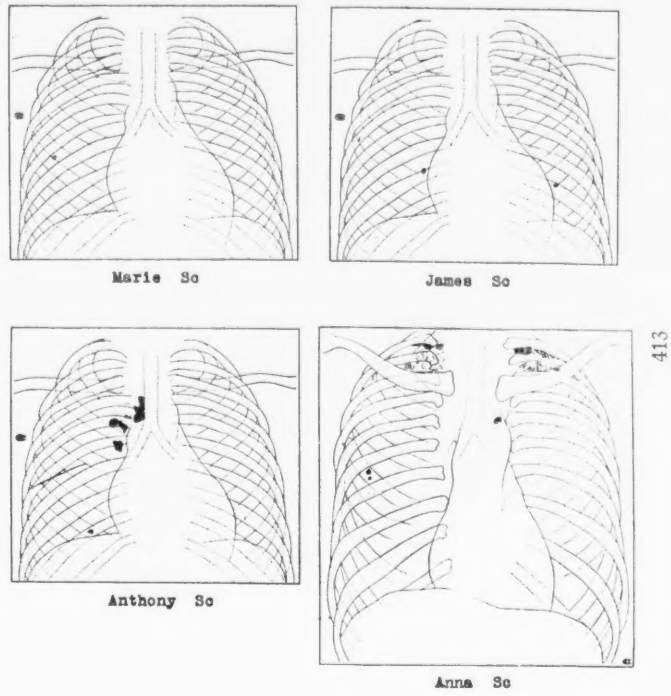

Marie Sc
James Sc
Anthony Sc
Anna Sc

FIG. 30

Figures 31 and 32

Family Cl: Probable source of infection: Father. *Duration of contact:* 8 and 11 12 years until April, 1926, continuing.

Pulmonary tuberculosis of the father: In May, 1917, Benjamin *Cl* came to the dispensary with ventral hernia. His chest examination was negative. Roentgenograms of December, 1925, show in the right and left apices irregular shadows, with salients and strands directed into the lung.

Latent apical tuberculosis of the mother: Mrs. Fannie *Cl* has no complaints and physical examinations are negative. Roentgenograms of January, 1926, show apical scars.

Tuberculosis of the tracheobronchial lymph nodes of children: (1) Sarah is well. Oblique roentgenograms of January, 1926, show two sharply defined nodules (calcified) in the left lung peripherally, and one on the right descending bronchus. No oblique film was made at the first examination, and the tracheobronchial lesion may have been present. (2) William is well. Roentgenograms of April, 1924, show a sharply defined nodule (calcified) in the right apex. Roentgenograms of March, 1926, show also granular masses, 0.6 x 0.3 cm. and 1.2 x 1.8 cm., near the right bronchus. (3) Mendell is apparently well. Roentgenograms of April, 1924, and March, 1926, show on the left a definite patch of interlacing lines at the third rib anteriorly; on the right, a sharply defined nodule (calcified), 0.5 cm., peripherally in the lung, and granular spots (calcified), the largest 0.7 x 0.5 cm. close to the left main bronchus.

Housing: Four rooms and bath for six persons. *Cleanliness:* Fair. *Diet:* Insufficient. *Financial status:* Poor.

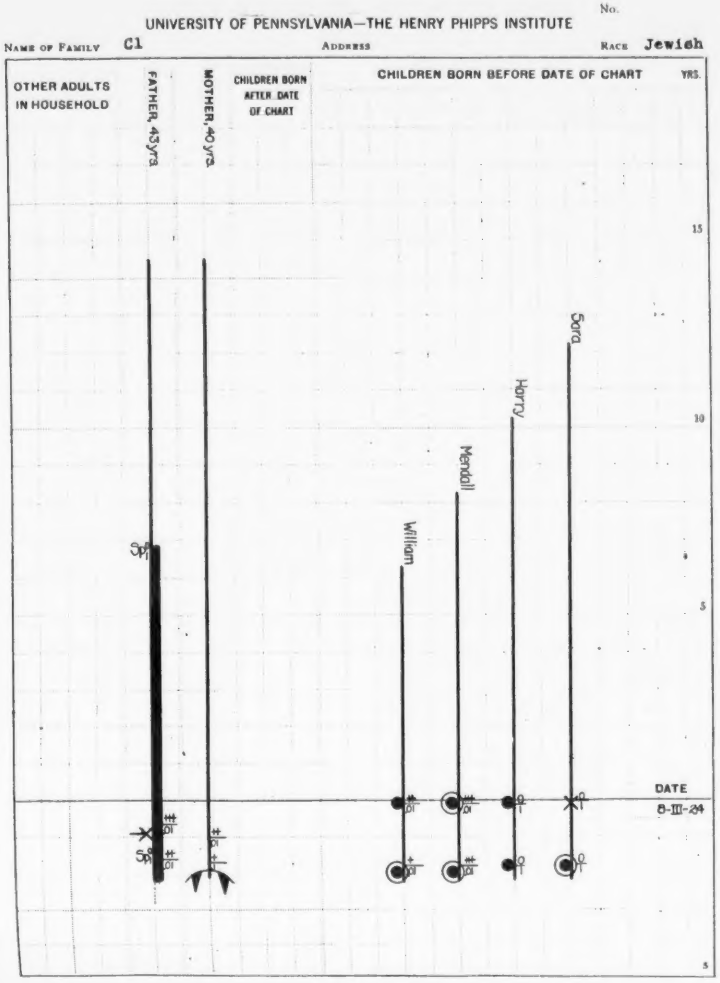
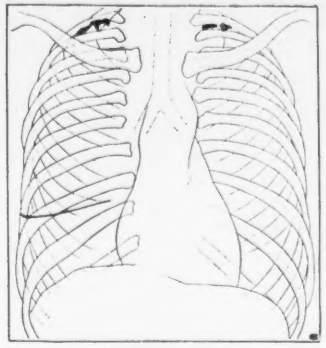
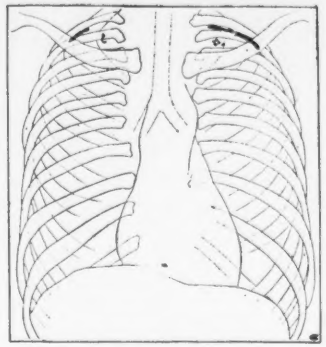


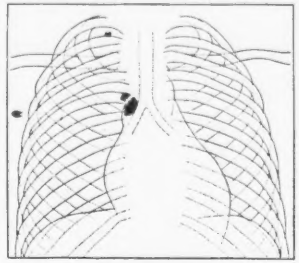
FIG. 31



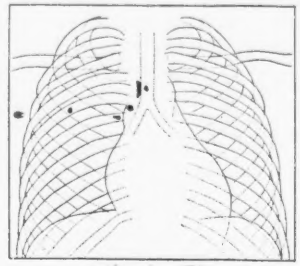
Benjamin C1



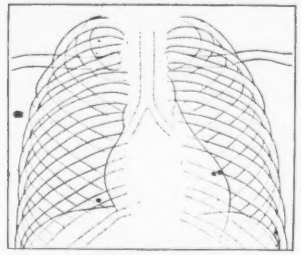
Fannie C1



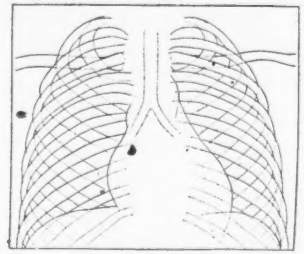
William C1



Mendall C1



Harry C1



Sarah C1

FIG. 32

Figures 33 and 34

Family Wa; Probable source of infection: Mother. *Duration of contact:* 16 and 6/12 years to May, 1926.

Pulmonary tuberculosis of the mother: Mrs. Dora *Wa* was first seen in May, 1911, reporting haemoptysis two years previously, cough and expectoration. Physical signs were those of a moderately advanced lesion. She was slightly underweight, but she gained weight rapidly. Roentgenograms of March, 1926, show on the left dense infiltration, with spots of calcification to the fifth interspace posteriorly, and below this an irregular noded network in places; on the right an irregular noded network occurs in places. This patient is probably not careful in disposal of sputum.

Latent apical tuberculosis of sister: Sarah's roentgenograms of November, 1923, and March, 1926, show a sharply defined nodule (calcified). In the right apex there is discrete mottling, and in the left there are shadows below the second rib. Physical examinations have discovered no abnormality.

Deaths of other children: Two children are dead. One died, aged one year, in 1913 of reputed pneumonia following whooping cough; one in 1915, aged 1 and 6/12 years, of malnutrition.

Housing: Four rooms and bath for four persons. *Cleanliness:* Fair. *Diet:* Sufficient, but in large part starches. The two children are definitely overweight. *Financial status:* Poor until recently.

Remarks: In view of the type and extent of the mother's lesion and her persistent fever, tuberculosis cannot be dismissed as the real cause of death in infancy of Paul and Israel. Kepple Wa, the father's son by a first marriage, lived for a time in this family. Later, at the age of 23 in August, 1923, pulmonary tuberculosis with positive sputum was recognized. There was no contact with this family at the time.

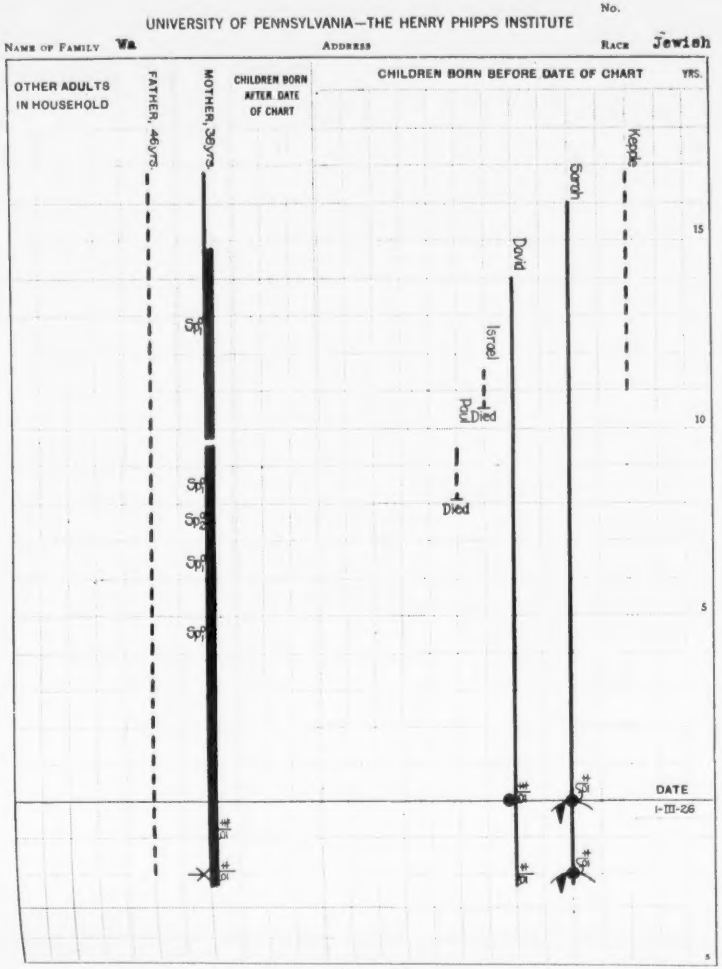
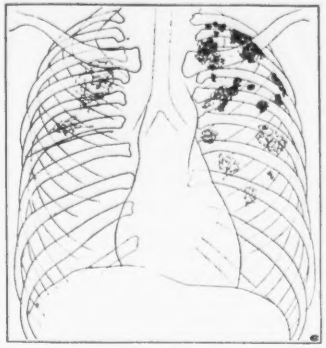
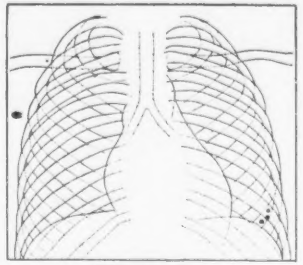


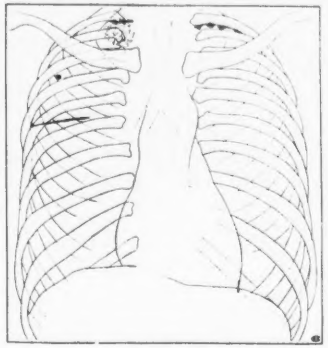
FIG. 33



Dora Wa



David Wa



Sarah Wa

FIG. 34

Figure 35

Family Wb: Probable source of infection: (1) Mother; (2) father. *Duration of contact:* (1) 7 years to March 1926. (2) 3 and 6/12 years to March, 1926.

Pulmonary tuberculosis of the mother: She was first seen in September, 1922, complaining of cough and expectoration for 3 years. Physical signs were those of a minimal lesion. Roentgenograms of March, 1924, and November, 1925, show a slight left apical scar and a fainter one in the right apex.

Possible pulmonary tuberculosis of the father: He was seen only once February, 1923, complaining of cough and expectoration for 4 months. Occasional fine râles were heard at the right apex. He has continued his work and is reported well.

Latent apical tuberculosis of a sister: Jennie has no sysmptoms referable to her chest. Roentgenograms of November, 1925, show a slight scar-like infiltration of the extreme right apex.

Housing: Six rooms and bath for seven persons. *Cleanliness:* Poor. *Diet:* Insufficient. *Financial status:* Poor.

Figure 36

Family Sb: Possible source of infection: Father. *Duration of contact:* 3 and 3/12 years to March, 1926.

Pulmonary tuberculosis of the father: When first seen, December, 1922, he gave a history of night cough for 3 months. Physical examination discovered a few medium coarse râles in the right apex. One week later on râles were found. The patient has been well. Roentgenograms of March, 1926, show a faint scar-like infiltration of the apex and the middle third of the right lung.

Housing: Six rooms for ten persons. *Cleanliness:* Fair. *Diet:* Insufficient and low in proteins. *Financial status:* Poor formerly, fair at present.

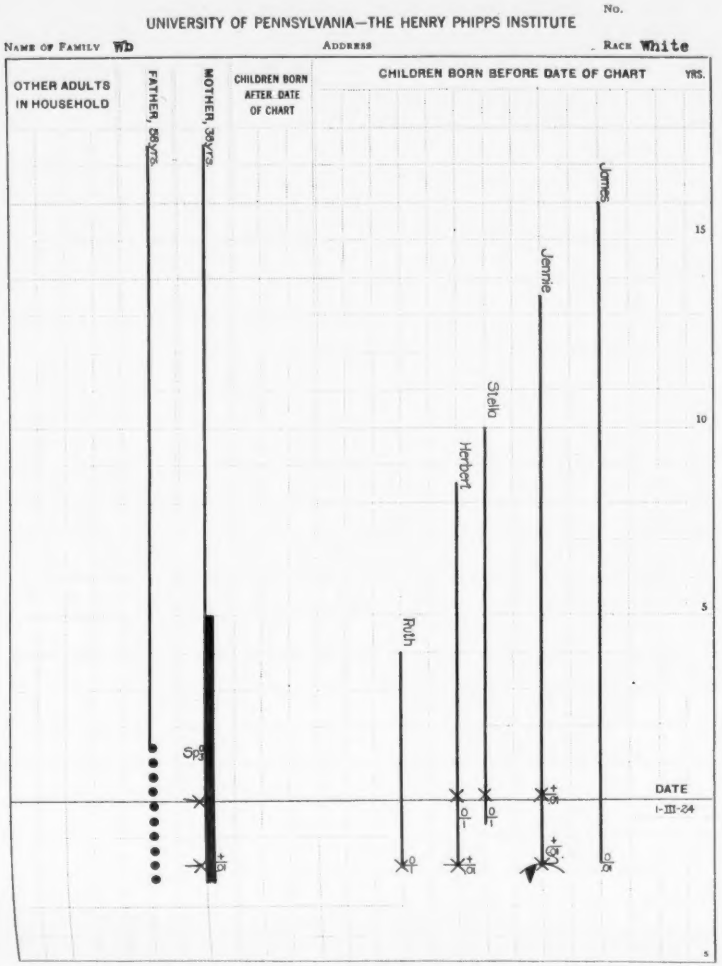

UNIVERSITY OF PENNSYLVANIA—THE HENRY PHIPPS INSTITUTE
No.
NAME OF FAMILY Wb
ADDRESS
RACE White
OTHER ADULTS IN HOUSEHOLD
FATHER, 59 yrs.
MOTHER, 39 yrs.
CHILDREN BORN AFTER DATE OF CHART
CHILDREN BORN BEFORE DATE OF CHART
YRS.
James
Jennie
Stella
Herbert
Ruth
Sp
DATE
1-III-24

FIG. 35

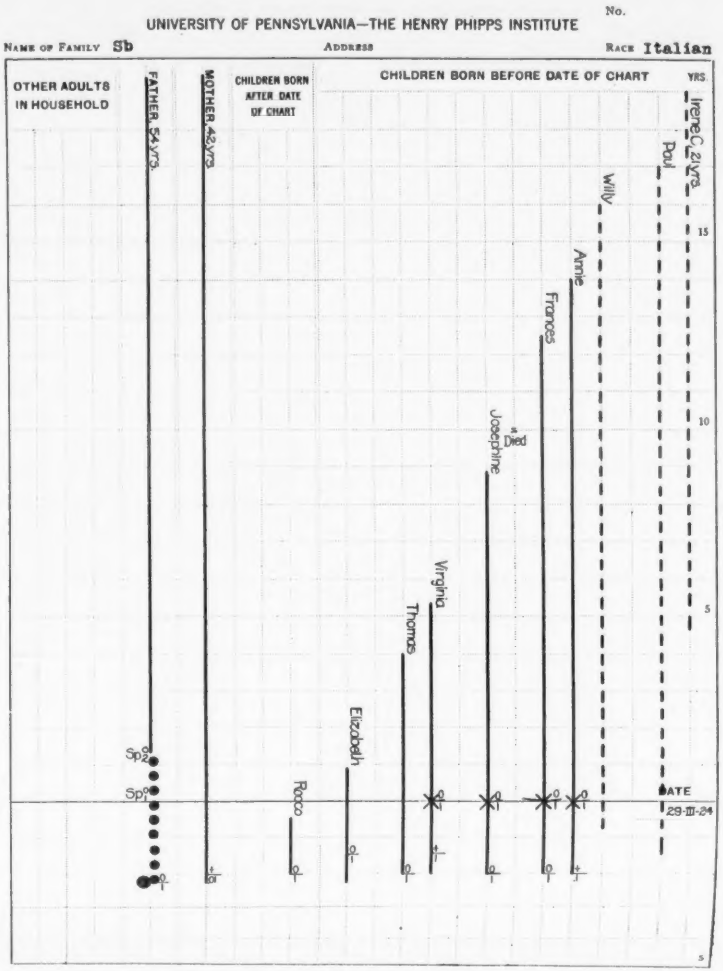

UNIVERSITY OF PENNSYLVANIA—THE HENRY PHIPPS INSTITUTE
No.
NAME OF FAMILY Sb
ADDRESS
RACE Italian
OTHER ADULTS IN HOUSEHOLD
FATHER, 54 yrs.
MOTHER, 42 yrs.
CHILDREN BORN AFTER DATE OF CHART
CHILDREN BORN BEFORE DATE OF CHART
YRS.
Irene, 2 yrs.
Paul
Willy
Annie
Frances
Josephine
*Died
Virginia
Thomas
Elizabeth
Rocco
Sp
DATE
29-III-24

FIG. 36

CLINIC RECORDS CONCERNING THE EXPOSURE OF CHILDREN TO TUBERCULOSIS[1]

L. F. RICHDORF AND A. E. HETZLER

This study of exposure to tuberculosis in children is a continuation of studies such as those of Myers and Magiera (1). These authors reviewed the histories of 2,000 children admitted to the Lymanhurst Out-Patient Clinic (2) (3) with symptoms suggestive of tuberculosis, and concluded that infection with tuberculosis could be demonstrated more frequently in children with a positive history of exposure. The purpose of this paper has been to study more intensively over a period of time a smaller group of children. The first 300 children admitted to the Lymanhurst Out-Patient Clinic were considered a suitable group for study, because 123 of these cases were seen one or more times after the first examination, at intervals of from a few weeks to two years. The majority of these 123 cases were observed not only in the out-patient clinic but also on the hospital ward or in the Lymanhurst School. That is, children (usually of school age) with symptoms suggesting a tuberculous involvement might be seen several times in the out-patient department. If evidences of a tuberculous infection were found, these cases might be referred to the Lymanhurst School or to the Hospital, depending on the severity of the symptoms. Certain cases in which observation was necessary were referred to the hospital ward for further study. After discharge from the hospital ward, children with evidences of tuberculous infection reported back to the out-patient department or entered the Lymanhurst School. In each of these departments a history was taken by the various physicians in charge. These histories were reviewed to determine the variability in history taking by different physicians, to note the physician's ideas of exposure to tuberculosis, and to note the effect of time in determining the diagnosis in adult contacts. After a careful examination of the original histories of the different physicians, and a summarization of succeeding follow-up records, a table was made to show the relation between exposure and infection in tuberculosis.

[1] From the Department of Pediatrics, University of Minnesota, and the Lymanhurst School for Tuberculous Children.

The first problem was to determine the variation in the histories taken by different physicians on the same case. In 78 of the 300 cases, written histories had been taken in two or in all three departments of this clinic. In 6 of the 78 cases an adult contact was diagnosed as tuberculous during the period of the child's observation. In 13 of the 78 cases the histories differed radically as regards exposure, the exposure being considered definitely positive by one department and definitely negative by another. This discrepancy may have been due, not only to a lack of appreciation by the patient or guardian of the meaning or importance of the questions asked, but also to the fact that the histories were procured from different members of the family. From what was recorded in the histories in 11 of the 13 cases (about one in seven), it appeared to be due to a hazy conception on the part of the doctor of what constitutes positive exposure, and consequent irrelevant questioning.

TABLE 1

Summary of adult cases of tuberculosis given as contacts in histories of 300 children

	DEATHS FROM TUBERCULOSIS	ACTIVE DISEASE	ARRESTED DISEASE	TOTALS
Mothers	23	31	2	56
Fathers	20	44	1	65
Sisters	4	8		12
Brothers	3	9		12
Other relatives	4	4		8
Total	54	96	3	153

The next step, after determining the variability in history taking, was to tabulate from the 300 histories the contacts regarded as a source of positive exposure by the doctor taking the history (table 1).

It is worth while to examine other qualifying statements given in the histories but not tabulated above. Such statements as the following were made concerning only 4 of the 23 mothers who died of the disease:

One: "died one year ago."
Two: "died recently." One of these mothers "slept with the child before she died."
One: "died six years ago."

Of the 31 mothers having the disease:

Five: "were at sanatoria."
Two: "were in families with other cases."
One: was diagnosed "after the death of husband."
Twenty-three cases: history was only "mother has tuberculosis."

Of the two mothers with arrested disease both "were discharged from sanatoria."

Of the 20 fathers who died of tuberculosis:

Two: "died recently."
One: "died three years ago."
Two: "died four years ago."
Three: "died six years ago."
One: "died at the age of forty-six years."
Eleven cases: only "father died of tuberculosis."

Of the 44 fathers having the disease:

Ten: "were at sanatoria."
Two: "were diagnosed two years after the children were first examined."
One: was a "registered case."
Three: "other members of the family had the disease."
Twenty-eight cases: no other details.

The one father with arrested tuberculosis was well twelve years after the first diagnosis.

Of the three brothers who died:

One: "died recently."
One: "died with three (?) other brothers at a sanatorium."
One: no other data.

Of the 9 brothers with the disease:

One: "has involvement of the bone."
Eight: no other data.

Of the 4 sisters who died:

One: "died recently."
One: "died at the sanatorium."
Two: no other data.

Of the 8 sisters having the disease:

Two: "were at sanatoria."
Six: no further data.

Of the 4 other relatives dying of the disease, there were

Two uncles.
One grandmother.
One "relative."

Of the 4 other relatives with the disease, there were

One aunt, "who lives with children coming to the clinic."
Two grandfathers.
One uncle.

From the above it is obvious that there is a necessity for an accepted definition of what constitutes exposure. Exposure is contact with the tubercle bacillus from any source. From a practical standpoint the history of exposure should determine the following: (1) the confirmation of the diagnosis of the disease in the contact; (2) the possibility of the excretion of the bacilli from the contact; and (3) the type and length of exposure.

In our histories of exposure even the confirmation of the disease in the contact was at fault. The diagnosis of the disease was probably correct in the contacts: (1) those said to have died of tuberculosis; (2) those with other members of the family having the disease; (3) those said to have been at sanatoria, or in sanatoria at the time of the examination of the patient; (4) in a majority of those said to be active. This would be 55 in group one, 6 in group two, 17 in group three, 35 to 40 cases in group four, or about 115 cases. As to the possibility of the excretion of the bacillus by the contacts, no definite estimate can be made. The 115 contacts noted above may have, during their activity, coughed up and expectorated living bacilli. But from the histories given, it is impossible even to say that the contacts were active or open at the time they lived with the children. The type of contact can be conjectured, only in a general way, as that usual in family life. However, many things which would affect exposure, such as the length of time that the patient had symptoms before diagnosis, the coöperation of the patient after diagnosis, and the home methods used for isolation, are not even mentioned. Because of inadequacy of the history of exposure, a new routine form was drawn up for the original history on each patient. This embraces the name and address of the contact, age and year when diagnosed as tuberculous, evidences of the disease, sputum examination, date of examination and result, and the type and duration of exposure. Also, since January, 1926, follow-up records on exposure have been particularly stressed on the "return" case. This has given additional information on the progress or the occurrence of tuberculosis in adult contacts in the environment of the 123 "return" cases. These cases have been seen two to five times over periods ranging from two weeks to four years. In the families of

these children the following changes, as regards tuberculosis in adult contacts, were noted:

Four deaths:

One, a mother who was ill with the disease when her children were examined.
One, a sister who was at the sanatorium when her brothers or sisters were first examined.
Two brothers (different families) not diagnosed at the time of the examination of the younger children.

Twelve with active disease:

Four fathers (one diagnosed two years after the examination of the children).
Two mothers (one diagnosed soon after her husband died of tuberculosis).
Two brothers.
Two sisters.
Two aunts.

Thus, in one out of about 30 children under observation because of symptoms suggestive of tuberculosis, a death occurred in an adult contact; also in one out of 10 such children, active tuberculosis was diagnosed in a member of the family or a close relative. In the majority of these contacts (14 of 16) the children were examined for tuberculosis before the adult contact was diagnosed, emphasizing the fact that studies of exposure to tuberculosis in children necessitate a knowledge of the condition of adult contacts over a period of several years.

In this paper, to recapitulate, the variability in histories of exposure taken on the same patient by different physicians has been shown; the data given in the original histories concerning adult contacts considered a source of positive exposure have been tabulated and analyzed; and the changes in the tuberculosis status of the adult contacts in the 123 "return" cases have been noted.

Following the above an attempt was made to show the incidence of tuberculous infection in children with a positive history of exposure (see table 2). By infection, or more correctly evidences of infection, is meant a positive tuberculin test, or positive findings in the X-ray plate, either the adult type of pulmonary lesion or a primary focus. The tuberculin test was done according to the method described by Pirquet (4). After cleansing with ether the volar surface of the forearm (part free from hair), two drops of fresh tuberculin are placed on the arm about four inches apart. Scarification is then done with the cleaned, dry Pirquet scarifier, first at a control point midway between the two drops and then in the two drops, care being taken not to cause bleeding. The tuberculin is allowed

to remain in contact for ten minutes, during which time the patient is cautioned not to move the arm or touch the areas; then, if not dry, the excess tuberculin may be removed with cotton. In younger children the areas of scarification are usually protected for several hours by a small piece of cotton held in place by a strip of adhesive. The extent of redness and infiltration of the control and tuberculin scarification areas are noted after forty-eight hours. If the control area shows a reaction this is noted, though usually there is very little redness about this area and all that is necessary is to measure the redness of the areas receiving the tuberculin. The reaction, to be considered positive, should extend out at least one-eighth of an inch beyond the scarified areas. Seven days after the application of the test the arm is again examined for redness and infiltration and also for beginning pigmentation. Pigmentation, even when no other reaction has been noted in forty-eight hours, is considered of diagnostic importance in the test. In very positive reactions, of course, pigmentation may persist for weeks or even months over the two areas of scarification receiving the tuberculin.

Positive exposure (table 2) was determined to some extent by the writers as well as by the individual physicians taking the histories. Inasmuch as one of the writers examines regularly in the out-patient department of this clinic, many histories of exposure were checked by him personally. Further, the writers had at their disposal histories taken on the same patient in three departments of the clinic, as well as the follow-up records, and were therefore able to check the accuracy of the histories in about one-third of the cases.

It is well to keep in mind the difference between table 2 showing the *children* with positive, negative or questionable exposure, and table 1 showing the *adult contacts* to whom the children were exposed. It happens that there were 153 contacts given as a source of positive exposure (of whom probably 115 had active tuberculosis), and 155 children with a history of positive exposure. These two figures do not need to correspond, and it is accidental that they do, inasmuch as one open case of tuberculosis might expose a number of children in a family or similar group.

Table 2 shows that 52 per cent of the 300 children coming to this clinic were considered to have had a positive exposure. Not all of these cases had a recorded tuberculin test or X-ray, but of the 148 with the tuberculin test, 70 per cent were positive, and of 100 children X-rayed 37 per cent showed a primary focus. The percentage of positive exposures in

this group is very high, inasmuch as the first 300 cases admitted after the opening of the Clinic were apt to be cases in greater need of attention than those admitted later. In comparing the exposed group with questionable and negative-exposure groups, primary foci and positive Pirquet tests occur at least twice as often in the exposed group. Thirty-seven of the 45 cases showing primary foci in the X-ray had a positive Pirquet. Three cases of adult type of fibroid tuberculosis were noted on the X-ray in the exposed group and also one case of bone tuberculosis (involvement

TABLE 2

Summary of exposure to tuberculosis in 300 cases at the Lymanhurst Clinic

	TUBERCULIN TEST			X-RAY								
					Primary foci		Peribronchial infiltration		Adult tuberculosis		Bone tuberculosis	
	Number done	Number positive	Per cent positive	Number done	Number present	Per cent present	Number present	Per cent present	Number present	Per cent present	Number present	Per cent present
Positive exposure												
155 cases or 52 per cent of total	148	101	70	100	37	37	8	8	3	3	1	1
Questionable exposure and no record of exposure												
31 cases questionable exposure	38	8	21	21	2	10	1	5	0	0	0	0
9 cases, no record of exposure												
40 cases in all, or 13 per cent of total												
Negative exposure												
105 cases or 35 per cent of total	98	36	37	49	6	12	7	14	0	0	0	0
Total 300 cases.....	284	145	51	170	45	27	16	9	3	2	1	0.6

of the femur). One of the 3 cases of the adult type of tuberculosis was considered active, showing râles and toxic symptoms. The equal incidence of peribronchial infiltration in the X-rays of both the exposed and nonexposed groups, and the lack of correlation of this finding with the signs of infection tend to discredit the view that this finding is diagnostic of a tuberculous process.

CONCLUSIONS

1. Histories of exposure to tuberculosis, taken by different physicians on the same case, vary widely.

2. Pertinent information is often not recorded because there is no commonly accepted definition of exposure.

3. Exposure is contact with the tubercle bacillus from any source, human or animal, inside or outside the family.

4. The history of exposure to tuberculosis should record the following:

(a) The existence of the disease in some person or persons with whom the patient has been in contact.

(b) The possibility of the excretion of the tubercle bacillus from such persons.

(c) The type and duration of contact between the patient and the persons having the disease.

5. The value of a history of positive exposure to tuberculosis depends upon our ability, or at times our opportunity, to diagnose the disease as both active and open in adult contacts.

6. In the group of children studied, evidences of infection with tuberculosis occurred twice as often in the exposed as in the nonexposed group. Children showing primary foci in X-rays of the lungs usually, but not always, gave a positive Pirquet test.

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STUDIES ON TUBERCULOSIS IN INFANCY AND CHILDHOOD[1]

VII. SERIAL EXAMINATIONS OF CHILDREN WITH EVIDENCES OF PRIMARY FOCI[2]

E. LEGGETT, DOROTHY HUTCHINSON AND J. A. MYERS

Ghon (1) is of the opinion that the primary tuberculous focus is a part of the reaction to primary infection, and that the primary complex consists of the focus plus the changes in the regional lymph nodes and connecting lymphatics. The primary focus is located at the point of entry of the infection, where specific inflammatory changes take place. Howell (2), Spitz (3), and others have also pointed out that these changes result in tubercle formation with caseation, and later fibrosis and calcification. The lesion, according to Ghon, is subpleural in location, is found more frequently in the right than in the left lung, and is most often in the lower lobe. When the reaction has gone on to calcification, the presence of the lesion is demonstrable by X-ray examination. The primary focus, as shown on postmortem examination, has been described by Ghon (4) as a small grayish area the size of a mustard seed or pea. It can usually be felt as an indurated area in the lung tissue and is subpleural in location. Canti (5) describes it as follows:

> The focus commencing as a small tubercle soon increases in size and involves the neighboring structures. Around it small anatomical tubercles may frequently be seen and fibrous tissue may be formed in an attempt at encapsulation. In the larger foci caseation usually takes place, which is hard and dry rather than soft and liquid, but occasionally a cavity is formed. The process may be arrested at any one of these stages as evidenced by fibrosis or calcification.

Bartlett and Wollstein (6) have shown that the lesion is usually too small to be demonstrated by physical examination. If there is a pul-

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[2] This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

monary focus the lymph nodes draining that area are involved. If there is a tuberculous lesion in the lymph nodes there is usually a corresponding pulmonary lesion. The location of the primary focus can be predicted from the nodes involved.

Ghon (4) and his followers consider that the lesion in the parenchyma always precedes the involvement of the lymph nodes, unless the portal of entry was extrathoracic. They believe that the focus in the lung is always present, although it may be missed due to faulty technique or lack of persistence. The foci are often small and difficult to find. Wollstein and Bartlett (7), on failing to find a parenchymal lesion, consider the primary lesion to be in the bronchial nodes. They believe that the tubercle bacilli may pass through the lung substance, without leaving demonstrable lesions, and localize in the nodes. This theory is also supported by the work of Krause (8). It is believed by Ghon (9) and by Bartlett and Wollstein that in the majority of the cases investigated the infection was acquired through inhalation. In such cases the bacilli are carried to the walls of the alveoli, where they are taken up by phagocytes which may pass through the lymph channels to the regional lymph nodes. In the lung are two sets of lymphatics, a superficial set supplying the pleura and a deeper set accompanying the bronchi and blood vessels. Chadwick (10) has called attention to the fact again that these two are connected and converge in the lymph nodes at the hilum. All drainage in the lungs passes to the tracheobronchial nodes. The bacilli-laden phagocytes may be arrested at any point along their course, in the alveolar wall, in the lymph vessels or in the lymph nodes. Baldwin and Gardner have shown in inhalation experiments that the lymph-node tubercle may become visible before that in the parenchyma of the lung; and Krause (23), that after primary *subcutaneous* inoculation of the guinea pig, early tuberculous changes are more prominent in the tracheobronchial lymph nodes than in the pulmonary tissue itself. This may be explained by the mechanism described above. Bacilli from a large area of lung are drained into the lymph nodes. If the infection is massive, and a large number of bacilli reach the lung at the same time, the lymphatics may be unable to carry them all away and a local lesion in the pulmonary tissue results. A local lesion may also result if the bacilli-laden phagocytes are arrested at any point along the course of the lymphatics. Infection in the tracheobronchial nodes may result from extrapulmonary lesions. The bacilli in the bloodstream may pass through the walls of the capillaries into the lymph

spaces of the lung, and from there be conveyed to the tracheobronchial nodes.

A specific inflammatory reaction takes place about the point of infection, and the lesion progresses until caseation takes place together with accompanying proliferation of fibrous tissue. In very young children Bartlett and Wollstein (6) have found no walling off of the infection. Though it may be quiescent, the focus is not encapsulated and rarely remains single for many months. When the focus is located in a lymph node, the node may or may not be enlarged, and the tuberculous lesion may occupy all or only a part of the node substance. In an older child or in an adult the lesion is usually walled off or encapsulated. Further development of the lesion may be in one of three directions. It may remain as a caseating focus, which later breaks down and becomes a source of reinfection to the body. It may become calcified, or it may be absorbed and disappear completely. Calcification, according to Amberson (11), signifies a well-established stage of reparation. It may be confined to small areas. It is accompanied by continued condensation and contraction, until finally there remains only an opaque nodule, with sharply defined borders, standing out in the roentgenogram in contrast to the neighboring shadows. In Amberson's experience the roentgenogram has never demonstrated the absorption of calcified deposits. There has been much discussion concerning the clinical significance of areas of calcification in the hilum nodes. Pancoast and others (12), in the report of the Research Committee of the National Tuberculosis Association, state that "calcified nodules at the root of the lung without evidence of lung disease are of no significance except as possible evidence of some healed inflammatory condition, possibly but not necessarily tuberculosis." Eberson (13), on the other hand, believes that "calcification of the lymph nodes ranging from beginning deposits to complete calcification may be regarded as indelible stigmata of tuberculosis." Achard (14) calls attention to the fact that calcified deposits have been demonstrated (by Rabinowitsch and others) to contain living and virulent bacilli capable of producing tuberculosis in guinea pigs. Caseous foci which are incompletely walled off are a frequent source of generalized tuberculosis. Gardner (15) has shown experimentally that lesions which have progressed to caseation and fixed-tissue cell proliferation may be absorbed, and leave no trace other than a microscopic scar. It has not yet been demonstrated that human pulmonary tuberculosis can heal by resolution, but experienced clinicians

have seen lesions disappear and leave no trace which can be detected by X-ray or physical signs, and it is not unreasonable to believe with Bendove (16) that many primary infections in the human body may disappear and leave no visible alteration in the tissues. Krause (17) supports Gardner's findings by citation of experiments in rabbits in which the disappearance of the lesions occurred six months or more after inoculation. With such resolution the animal may lose much of the immunity which it acquired from the primary infection.

The effect of the primary infection upon the resistance of the animal to subsequent reinfection is very important. Trudeau, Roemer, Krause and many others have shown that primary infection results in an increased resistance to reinfection. The animal is able to ward off more bacilli in such a manner that the normal anatomical response is modified. The resulting lesion may be so slight that no infection can be said to result, or the response is an acute inflammatory reaction which will tend to fix the bacilli *in situ*. As tissues become infected their capacity to react changes. Reaction to first infection always eventuates in the formation of focal tubercle. In reinfection there is an immediate reaction with acute inflammation, which subsides, and anatomical tubercle supervenes. Allergic or sensitized animals over-react to reinfection. If the reinfection is massive diffuse types of tuberculous lesions occur. In animal experimentation the immunized animals either die rapidly when exposed to massive reinfection or recover. Those animals which recover do not later succumb to the infection as do the nonimmunized animals. Healing of the primary infection, with absorption of the focus, is accompanied by a diminution of allergy (and presumably immunity), as shown by the tuberculin reaction. (See Krause (18).)

Though a primary infection increases the resistance of the body to reinfection, the primary focus may serve as a source of reinfection. With a focus latent or inactive the individual is protected by its fibrous investment from the bacilli within it. To produce symptoms of disease the tubercle must give up something of itself to the body. The degree of fibrosis and sclerosis is one of several factors that determine the amount of circulatory exchange between focal interior and surrounding tissue. Any condition which establishes new or enhanced communications between tubercle and surrounding tissues promotes an increase of symptoms. In young children the nature of the investing wall is often such that communication is easily established. In an adult the walls tend to be less pervious and the primary focus is, in general, not so

serious a source of danger. Local inflammation about the lymph nodes in bronchitis, measles, colds, etc., which result in congestion about the tuberculous focus, may bring about reinfection from a focus, or cause a previously quiescent lesion to become active. Extension from the primary leson may be direct. It may result from the rupture of a caseous node into a blood vessel or bronchus. Extension may be through the lymph channels. The mechanism of the extension from a lesion in the periphery toward the hilum is easily understood. Extension from the hilum to the periphery is explained by Honeij (19) as follows:

When tuberculosis develops in a hilum gland which receives a bronchial vessel the resulting inflammation tends to block that vessel. The lymph finds a new outlet and passes by means of anastomoses into neighboring vessels.

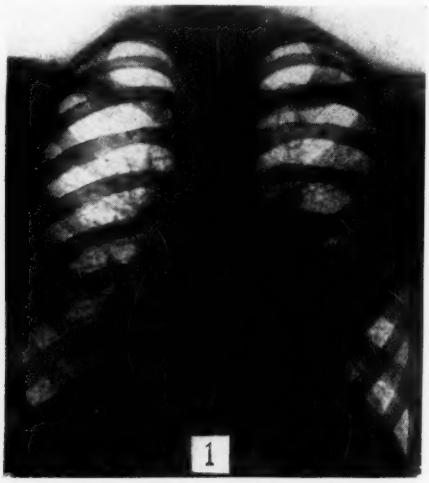


FIG. 1. R. B., AGE 8, APRIL 20, 1925

Note the calcified primary focus in the second interspace on the left side. The enlargement and calcification of the hilum nodes is more marked on the left side.

The lymph flow between the anastomotic areas is reversed. Any tubercle bacilli escaping from the affected gland travel outward. On reaching the relatively narrow anastomotic vessels they become arrested and give rise to tubercles in the lung parenchyma. Ghon and Kudlich (20) report six cases of endogenous reinfection from exacerbation of a tuberculous process in some lymph node at the hilum. Baldwin and Gardner (21) state that after primary infection "later inhaled or ingested bacilli are resisted more or less strongly by the relative immunity from infection." But mild infection occurring frequently may by cumulative effect ultimately arouse the diseased process.

In 1925 attention was called (22) to a desire to make serial examinations of children showing evidence of primary lesions. The object of our work, of which the present paper is only a preliminary report, therefore, is to study over long periods a group of children with evidence of primary tuberculous foci, with the hope of learning more about the history of the stages through which such processes pass. Our cases are selected from the out-patient department of the Lymanhurst School for Tuberculous Children. All cases are requested to return every six months for reëxamination except those in whom more frequent examinations are desirable. The examinations include histories, tuberculin tests, physical and stereoscopic X-ray plate studies.

The appearance of the area usually interpreted as a primary focus in the X-ray examination of the chest of the patient is shown in figure 1, in which it appears as a small area interpreted as calcification in the second interspace on the left side; it is subpleural in location and is not surrounded by bronchial markings. The location of the foci in our group of cases is as follows:

Right upper lobe	9	Left upper lobe	13
Right middle lobe	3	Left lower lobe	13
Right lower lobe	17		
Total right	29	Total left	26

In all cases the focus was apparently calcified, and in the serial plate showed no changes in density which could not be accounted for by differences in X-ray technique. In all cases the hilum nodes showed evidence of enlargement, and in all except three evidence of calcification. The calcification was usually more marked on the side of the primary focus. The size of the foci varies from that of a bean to that of a pea. Three cases showed two or more foci.

Perhaps such findings represent the end-results of primary tuberculous lesions. Although we have observed no changes in the findings since the beginning of this study, it is our intention to observe them over as long periods of time as possible. It is hoped that some cases may be followed into adult life.

The earlier stages of primary tuberculous lesions need further study. If a case is seen only once or twice the process may look so badly as to warrant a grave prognosis. Indeed we have seen several such cases. However, as we come to know the various stages through which such lesions may pass we become better able to interpret the findings, when for some reason we are allowed to make only a single examination of a

case. Figures 2 to 7 show lesions in a case which at times seemed to warrant a bad prognosis. Yet, if the case were seen at the time figure 7 was made, or at any time since, the examiner would have no conception of the extensive stages through which the lesions had passed. Our interpretations of X-ray findings in certain stages in this case might be questioned, but only postmortem examination could prove conclusively the actual condition. Nevertheless, the shadows cast now are those usually interpreted as representing old primary tuberculous foci.

It is well known that some primary tuberculous lesions do not undergo healing as seen in figures 2 to 7, but that they result in the death of the child. On the other hand, we are convinced that some may heal by resolution, leaving in future years no demonstrable trace of their former existence. The subsequent history in such cases we do not know. Perhaps they are just as susceptible to tuberculosis as before the primary lesion occurred. But, since the type of primary focus that leaves evidence of its existence may be a source of subsequent disease, its early recognition is important. Children with such primary foci should be given special care. Their general resistance should be built up by proper living conditions. Nontuberculous infections affecting regional lymph nodes must be guarded against. All of this we are trying to do with our cases at the Lymanhurst School for Tuberculous Children, and in

Figs. 2 to 7. Serial films of same child

FIG. 2. C. D., AGE 4, MARCH 31, 1923

Note the definite parenchymal infiltration along the vertebral trunk in the left upper lobe and in the third interspace. On the right side the dense central shadow probably represents a mediastinal pleurisy associated with a pleuritic involvement of the interlobular septum.

FIG. 3. NOVEMBER 20, 1923

Note the area of increased density persisting in the left third interspace, with slight calcium deposit in the hilum nodes on the left side. The shadow extending from the second to the sixth ribs on the right is interpreted as a primary tuberculous bronchopneumonia.

FIG. 4. JANUARY 2, 1924

The greater portion of the right lung shows evidence of infiltration. There is slight clearing in the right lower lobe. Note the dense area opposite the third rib on the left and the calcification of the hilum nodes on the same side.

FIG. 5. JANUARY 14, 1924

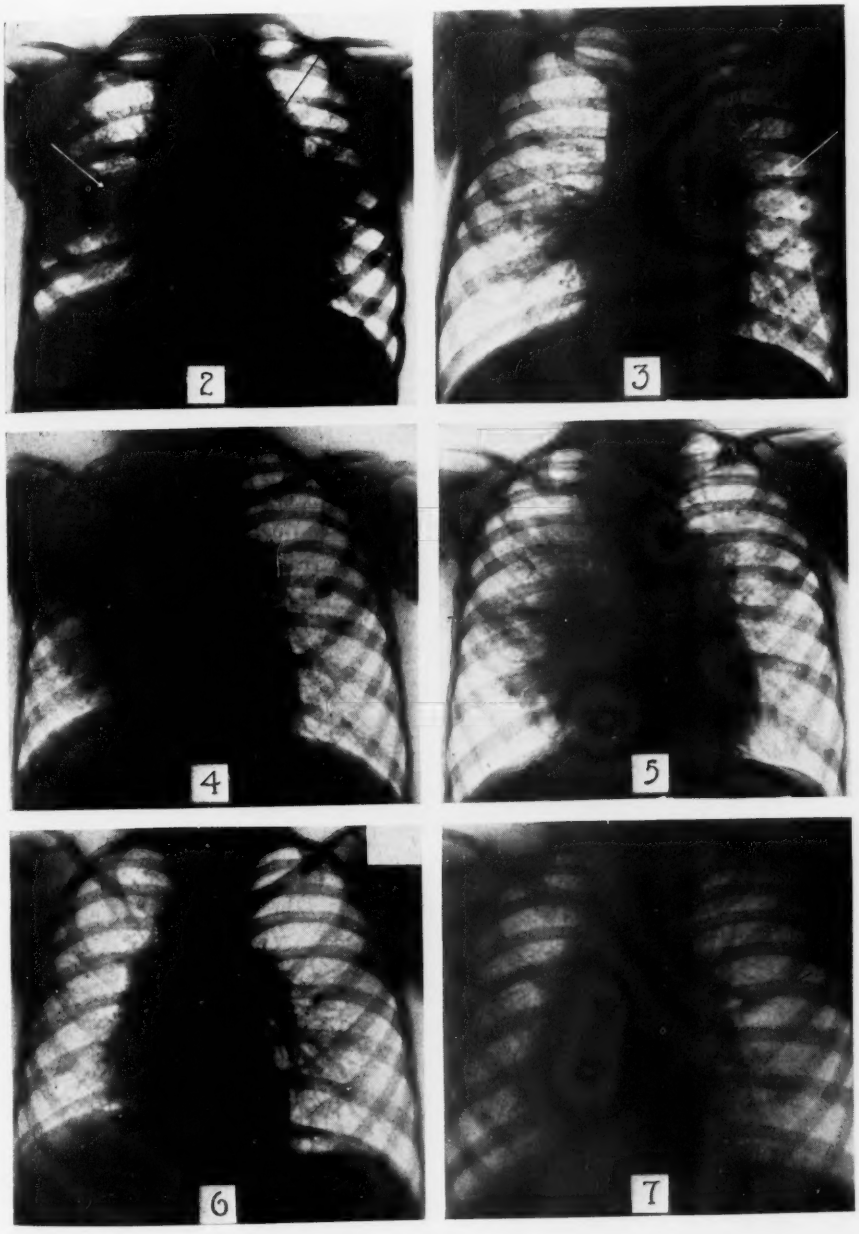
Note the clearing of the condition in the right lung with slight retraction of the mediastinum to the right. The calcified area opposite the third rib on the left side persists, as does the calcification of the hilum nodes on the left side.

FIG. 6. SEPTEMBER 25, 1925

The right parenchymal lesion has continued to clear and the hilum shows calcification. There is slight irregularity of the diaphragm on the right, and the mediastinum is drawn somewhat to the right. The remains of a primary focus are seen opposite the third rib on the left. Note the large calcified hilum nodes on the left side.

FIG. 7. OCTOBER 20, 1925

Note the calcified areas in the right and left lungs. These are interpreted as representing the end-results of primary tuberculous foci.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the meantime we are trying to learn more about the history of their tuberculous processes.

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STUDIES ON TUBERCULOSIS IN INFANCY AND CHILDHOOD[1]

VIII. SERIAL EXAMINATIONS OF CHILDREN WITH PULMONARY LESIONS[2]

DOROTHY HUTCHINSON AND J. A. MYERS

The work of Krause (1) on *Human Resistance to Tuberculosis at Various Ages of Life* has greatly stimulated interest in the study of cases over long periods of time. Some of his cases under observation for many years have made it possible for him to prove facts regarding this disease which differ greatly from our former beliefs and opinions. This is particularly true of the healing, and in some cases of the complete disappearance of tuberculosis.

Every physician who treats tuberculous patients sees many who have unmistakable tuberculous lesions in the lungs,—lesions causing symptoms, but which disappear, leaving no sign of their existence, and such patients are restored to good working capacities. Serial examinations by Stewart (2), Amberson (3), Webb (4), and Bendove (5), made on patients suffering from pulmonary tuberculosis, have shown that fairly extensive lesions may become so removed as to leave little or no evidence of their former existence. Moreover, Gardner (6) made a most important contribution when he presented the histological mechanism of the process of healing. Using the well-known R1 strain isolated by Trudeau in 1891, Gardner proved conclusively that tuberculous lesions may heal by resolution, and heal so completely as to leave a perfectly normal histological appearance of the involved lung and pleura, except for a lymphoid hyperplasia, which serves as the only indication of the previous disease.

The question arises as to whether pulmonary tuberculous lesions in infants and children may undergo such marked healing, and even complete disappearance as they do in adults. Indeed, Harms (7) has already

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shown that healing by absorption does occur in infancy and childhood. The object of our study, of which this is a preliminary report, is to determine, in so far as possible, the course of pulmonary lesions in infancy and childhood. The Lymanhurst School and Hospital for Tuberculous Children offers an opportunity to observe such lesions from the date of their detection over considerable periods of time. The cases with progressive disease are sent to the Glen Lake Sanatorium; when their disease comes under control they are returned to the Lymanhurst School and Hospital. The medical staff of the sanatorium has been most cooperative in making it possible for us to carry on our observations during the patient's residence there.

The majority of our cases reach the Lymanhurst School through our tuberculosis dispensary. Others are sent to us by other dispensaries, private physicians, etc. Inasmuch as pulmonary lesions are not as frequent in childhood as in adult life, the number of cases with such lesions coming through a dispensary is somewhat limited. Again, not all pulmonary lesions observed are tuberculous. In this work we have taken all cases that have gone through our out-patient department, as well as those that have been in the Lymanhurst School, and selected from them all who showed evidence of pulmonary involvement of any kind. From our first observation of each case we have attempted to trace the course of the lesion. Obviously, it has not been possible in every case to obtain positive proof that the lesions are tuberculous.

In studying these children it was most interesting to find that frequently the younger ones made remarkable recoveries. In order to determine the effect of the disease at various ages we have made an arbitrary divison into three groups: first, from infancy to five years; second, from six to eleven years; third, from twelve to eighteen years. In the first group are 12 children, including 3 infants 10, 15 and 17 months of age. The second group contains 19 children; the third, 32 children. As would be expected, the incidence of disease increases with the age.

The diagnosis of pulmonary lesions in children is at times most difficult. As in older persons, the cardinal symptoms are at times present, such as frequent colds, loss of weight, fever, night sweats, weakness, chest pains and hemoptysis. It has been our experience, however, to find parenchymal lesions in children, demonstrable by X-ray, exhibiting few or no symptoms of their condition. These children have been sent to the clinic on account of exposure to tuberculosis. Of our series of 66 children, 4 have had hemoptyses, 2 of these being associated with cavitation.

These children are all in the third group (12 to 18 years). Thirteen cases had sputum positive for tubercle bacilli; these cases were also in the third group. Repeated inoculations of guinea pigs with stools and examinations of sputum of the younger children have all been negative. This is true even in the cases of cavitation, and in the one case of puerile tuberculosis with diffuse involvement.

The Pirquet tuberculin test is of diagnostic value to a certain extent, particularly in the younger cases. Forty-five positive and 16 negative reactions were obtained at the time of the first visit of the children to the out-patient department. Of the 16 cases having negative reactions, 2 proved to be nontuberculous acute infections; 2 showed peribronchial infiltration in an upper lobe, one of these patients having slight hemoptyses.

One infant, 15 months of age, had a negative reaction at the time of the first examination, which subsequently became positive. This child was examined on account of exposure to tuberculosis, the child having no symptoms of disease. The stereoscopic plates of the chest showed a definite parenchymal lesion in the second right interspace, while the physical examination was negative except for slight impairment of resonance at the angle of the right scapula. Approximately two months later the Pirquet reaction was found to be strongly positive, while a new X-ray of the chest showed resolution of the parenchymal process. Plates of 3 other children showed questionable upper-lobe lesions, none of these returning for reëxamination. One definite case of advanced pulmonary tuberculosis with cavitation reacted negatively to the tuberculin skin test, but a positive reaction was obtained three months later.

The remaining 7 children having negative reactions showed definite fibroid lesions above the third rib. Upon reëxamination 7 cases reacting negatively to the Pirquet test were found to have become positive. One was the case of far-advanced disease, another the infant mentioned previously in this paper. The third is a boy of fifteen years, having peribronchial infiltration in an upper lobe and coming to the clinic on account of hemoptysis. Three months after the first examination the Pirquet test became positive. Four cases remained negative to the tuberculin test, two, and in some cases three, tests being given. Two of these showed definite evidence of fibroid tuberculosis on X-ray, the other 2 having lesions of nontuberculous nature.

It must be borne in mind that one negative Pirquet test is not conclusive, many factors being capable of causing a negative reaction in a tu-

berculous child. As far as possible, such errors have been guarded against, and repeated tests made when possible. Koch's Old Tuberculin was used in these cases, many tests being given at one time, using the same material. As some positive reactions have been obtained each time, it is safe to assume that the material used was potent.

Cases of proved tuberculosis reacting negatively to the tuberculin skin test have been known. One especially interesting has been reported by Dr. Rachel L. Ash (8) of San Francisco. The child was exposed during the first six weeks of life to open tuberculosis in the mother. The disease progressed slowly, involving first the lungs and later the osseous system. The Pirquet and Mantoux tests were repeatedly negative, until the child was two years of age when they became positive. A staphylococcic infection of the mastoid developed, causing the death of the child. Tuberculosis of a chronic nature was revealed upon autopsy, involving both lungs as well as multiple lesions in the osseous system. Large cavities were found occupying the left upper and right upper lobes and having thick indurated white walls, a wide zone of fibrosis surrounding one of the cavities, while diffused conglomerate tubercles were scattered throughout the remainder of the lung tissue. Dr. Ash remarks "the presence of a negative von Pirquet in no way rules out the diagnosis in a child under two years of age."

It has been the commonly accepted idea for years that a body once infected by the tubercle bacillus will ever after react positively to the tuberculin test. This erroneous idea has been corrected by the observation of Krause (1) discussed recently in his *Human Resistance to Tuberculosis at Various Ages of Life*. Austrian (9) also has shown evidence proving this fact. Of 97 children given Pirquet tests in 1915 and 1916 and re-tests in 1920, 10.31 per cent formerly positive became negative, 15 per cent formerly negative became positive, while 10 per cent formerly negative remained negative to the tuberculin test (Austrian). Two cases of our present series in which the Pirquet test became negative were found. One, a girl eleven years of age, complaining of frequent colds and fatigue showed a few old fibroid deposits in the left apex. The Pirquet test was at this time faintly positive. Reëxamination seven months later showed improvement in the clinical symptoms. A negative Pirquet was obtained, although roentgen plates taken at this time showed the old fibroid deposits present as at the time of the former examination. The other, a girl of thirteen years, symptomless except for being underweight, showed fibroid involvement in the first and second

interspaces on the right side. A Mantoux test of 0.1 cc. of a one to five-hundredth solution of tuberculin was negative. It is desirable to repeat this test, using a stronger solution, but as yet this has not been done.

The physical signs in the great majority of our cases showed slight changes from the normal, or were indicative of a normal chest. This is especially true in the younger children. Slight impairment of resonance over one or both apices was the most frequent finding, while exaggeration of the normal puerile breath-sounds was fairly frequently found. Changes in voice-sounds occurred occasionally. Moderately coarse râles, following cough, so common in adult cases of tuberculosis, occurred rarely, although inconstant râles were at times heard over various parts of the chest and were of many types. However, 16 cases were found to have definite moderately coarse râles above the third rib, the majority of these being among the older children.

The X-ray plates are indispensable in the examination and diagnosis of lesions in children. It has been pointed out that the physical signs and symptoms were indicative of health or of so slight a nature as to be disregarded, while even the Pirquet reaction was at times misleading, but upon X-ray examination of the chest parenchymal involvement of considerable extent was found. It is a routine procedure at Lymanhurst Clinic to make stereoscopic plates upon admission, and repeated plates are made every six months unless more frequent examinations are indicated. In this way we have detected many of the lesions included in our present series of cases which would undoubtedly have been overlooked had the roentgenographic study not been made routinely.

The formation of cavities in children is not as infrequent as was formerly believed. Siperstein and Baugess (10) have collected 273 cases in infancy reported in the literature. Farmer (11) remarks that cavity formation in pulmonary tuberculosis in the first two years of life is not exceptional. Quoting from the literature, he gives reports of various articles: Ribadeau-Dumas (12), 1913, found cavitation in 32.37 per cent of his autopsies upon infants; White and Carpenter (13), 1909, 16 per cent, and Ghon (14), 1916, 43.75 per cent of his autopsies. The diagnosis of cavitation in infancy and childhood is at times most difficult. The case reported by Siperstein and Baugess (10) is to our knowledge the first reported in the literature in an infant that was diagnosed before death and confirmed by autopsy. The physical signs of cavitation are rarely found; indeed the case reported by Ash (8) showed no clinical evidence of cavitation, although one large cavity occupied practically the

right upper and middle lobes. Farmer (11) reports 7 cases of cavitation under two years of age, signs of cavitation being found in but one of these. This, however, could not be determined clinically until three weeks after the diagnosis was made by the X-ray picture and not until it occupied the greater part of the middle and lower lobes. One case with cavitation showed no abnormal physical signs suggestive of a pathological condition in the lung throughout the entire course of the disease. Thirteen cases of cavitation were found in our present series, 3 of these in the younger group and 10 among the older children. The 3 younger children were two, four and five years of age. The lesions found in these were all of a soft mottled type involving a considerable portion of the upper lobe. In all three, subsequent examinations showed a retraction of a lesion by fibrosis, with a disappearance of the cavity. One of our cases is interesting in that hospitalization was refused, the child receiving ordinary home care. He steadily improved, and the lung lesion was reduced in size, becoming fibrous while the cavity disappeared. Case reports illustrated by plates will be given of two of these children later in this paper. Of the 10 cases of cavitation among the older children, 2 were not visible upon later roentgenographic examination. One case with multiple cavitation in the left upper lobe proved later to be lung abscess rather than tuberculosis. Three children having cavitation have died, and 3 are at present receiving artificial-pneumothorax treatment.

The tabulation of the cases showing the amount of involvement and the subsequent condition of the children at the time of later examination will be found in table 1. The first group contains 13 children, 4 of which were found improved and 4 healed at subsequent examinations. Five of this group could not be traced for reëxamination. The second group contains 19 children; 6 of these were improved and 4 healed at a later examination. One died later, showing diffuse involvement of puerile type. Eight could not be traced. Of the 34 cases of the third group, 16 were found to have improved, one had become healed, 6 showed extension of the lesion, 4 had died, and 7 could not be traced. Thus a total of 66 children were examined. Of these, 26 (39 per cent) were found later to be improved; 9 (13 per cent) had become healed; 6 (9 per cent) showed progression of their condition; 5 (7.5 per cent) had died, while 20 (30 per cent) could not be traced for reëxamination. It will be seen, however, that these 20 cases all had minimal or questionable involvement, and would most likely have returned for further care had not their conditions been favorable. The 9 cases considered healed all showed a complete

disappearance or calcification of the lesions on X-ray examination, and with a disappearance of all clinical signs and symptoms, while the cases

TABLE 1

Pulmonary lesions in children

INVOLVEMENT	NUMBER	IMPROVED	HEALED	ADVANCED	DEAD	NOT TRACED	PIRQUET TESTS	
							First	Second
1 to 2 years:								
Minimal	4		1			3	4+	1+
M. A.	3	3					3+	2+
F. A.	1		1				1+	1+
Questionable	5	1	2			2	4+ (1N*)	3+
Total	13	4	4			5	12+ (1N)	7+
6 to 11 years:								
Minimal	12	4	3			5	8+ (4N)	3+ (3N)
M. A.								
F. A.	1				1		1+	
Questionable	6	2	1			3	4+ (1N)	1+ (1N)
Total	19	6	4		1	8	12+ (5N)	4+ (4N)
12 to 18 years:								
Minimal	22	15				7	14+ (8N)	8+ (2N)
M. A.								
F. A.	11	1		6	4		7+ (1N)	5+ (1N)
Questionable	1		1					
Total	34	16	1	6	4	7	21+ (10N)	13+ (3N)

Total of all groups

1 to 18 years:								
Minimal	38	19	4			15	26+ (12N)	12+ (5N)
M. A.	3	3					3+	2+
F. A.	13	1	1	6	5		9+ (1N)	6+
Questionable	12	3	4			5	8+ (3N)	4+ (2N)
Total	66	26	9	6	5	20	46+ (16N)	24+ (7N)

*N = negative.

showing fibrosis of a lesion or marked improvement of the general condition were classified as improved. Twelve were classified as questionable tuberculous cases. In this group were included indefinite upper-lobe lesions, such as peribronchial infiltration or bronchopneumonia.

In considering the result of this series of cases, it must be borne in mind that few were clinically ill at the time of examination, the children being sent to the clinic by the school or visiting nurse on account of exposure to tuberculosis, for malnutrition or some suggestive symptoms, the more acutely ill children being examined by the family physician. Perhaps, if the course of all cases of adult type of tuberculosis in children were followed, a higher percentage of deaths would be found. This study is of importance in showing the great number of mild cases which undoubtedly run their course undiagnosed, the majority of the cases improving and the true nature of the disease remaining unsuspected.

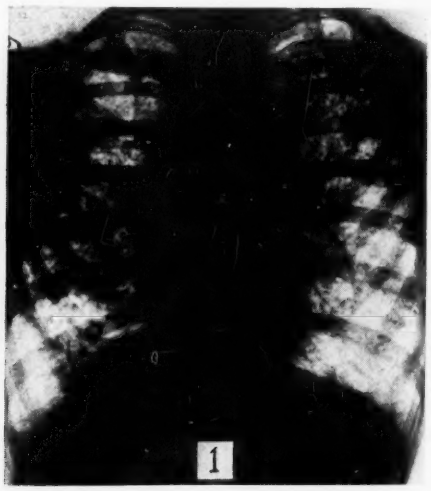

FIG. 1. ROENTGENOGRAPH OF CHEST OF A CHILD NINE YEARS OLD, TO SHOW PUERILE TYPE OF TUBERCULOSIS

Were roentgenographic plates of the chest made in the obscure low-grade ailments of childhood, we believe that many of the cases would show pulmonary lesions, and that many of these children could be greatly benefited by proper care, guarding them against breakdown in the later years when they meet the greater strain of life.

Case Reports

The following are reports of five cases with plates, showing the course of the disease to illustrate the results in some of the children.

Case 1: H. McK., age 14 years. Plates, made July 12, 1923, showed a fibroid tuberculosis disseminated throughout the left upper lobe, a small cavity in the first interspace. Plates, January 11, 1924, showed an acute consolidation in the left lower lobe, with an involvement

also of the right upper; the condition of the left upper lobe had not changed. At this time the child was suffering with symptoms of acute lobar pneumonia. The third plate, taken November 13, 1924, showed incomplete resolution of the pneumonic process with extension on the right side, the condition of the left upper lobe remaining unchanged. A localized pneumothorax could be seen in the left lower lobe. The process increased in this child, death occurring one month after the last plates were taken.

Case 2: J. Z., age 9 years. Admitted as an emergency case, March 12, 1925, with high temperature, cough and hoarseness. The plates of the chest showed the diffuse involvement seen in figure 1. This child died three months later of an extension of his disease.

Case 3: P. P., age 14 years. The first plate taken July 10, 1924, figure 2, showed a moderate enlargement of the hilum nodes on each side. A mottled fibroid tuberculous infiltration is seen in the right upper lobe with cavitation. Plates made December 3, 1925, figure 3, showed a marked decrease in size of the lesion, only a few fibroid strands remaining in the extreme apex. No evidence of the cavity is to be seen. This child has gained thirty pounds in weight, and is at present symptomless.

Case 4: A. H., age 5 years. Admitted to clinic, June 4, 1925, complaining of frequent colds and exposure to tuberculosis. The physical signs showed roughened breathing in the right apex, with bronchial breath-sounds and increased whispered voice in the left interscapular space. The first plate was taken June 4, 1925, and showed slight enlargement with moderate calcification of the hilum nodes on both sides. A definite parenchymal lesion involved the first, second and third interspaces on the right, with a questionable small cavity in the second interspace. The subsequent plates showed a gradual decrease in the size of the lesion and a disappearance of the cavity. Plates taken August 10, 1925, figure 4, and January 25, 1926, figure 5, are shown. The general condition of this child is at present excellent.

Case 5: I. W., age 2 years. Admitted on account of exposure to an open case of tuberculosis in the mother. X-ray plates, figure 6, showed localized pneumonia in the left upper lobe with a questionable small cavity Subsequent plates, figure 7, taken nine months later, showed a definite fibrosis of the lesion. The general condition of this child is excellent.

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FIG. 2. ROENTGENOGRAPH OF CHEST OF CHILD FOURTEEN YEARS OLD, TO SHOW MOTTLED FIBROID INFILTRATION RIGHT UPPER LOBE WITH CAVITATION

FIG. 3. SAME CHILD AS SHOWN IN FIGURE 2

Plates taken seventeen months later show the lesion reduced to a few fibroid strands in extreme apex with no evidence of cavitation.

FIG. 4. ROENTGENOGRAPH OF CHEST OF A CHILD FIVE YEARS OLD, TO SHOW PARENCHYMAL INFILTRATION IN FIRST, SECOND AND THIRD INTERSPACES, WITH A QUESTIONABLE SMALL CAVITY IN THE SECOND INTERSPACE

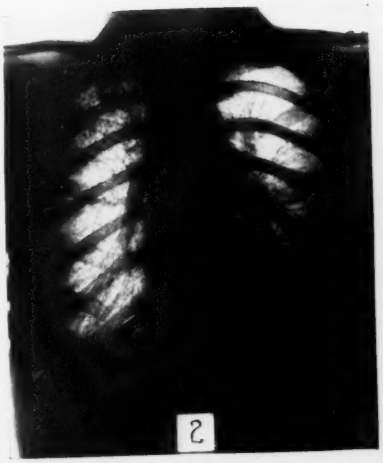
FIG. 5. SAME CHILD AS SHOWN IN FIGURE 4

The lesion is reduced to fibrous strands extending out from the hilum

FIG. 6. ROENTGENOGRAPH OF CHEST OF CHILD TWO YEARS, TO SHOW LOCALIZED PNEUMONIC AREA IN LEFT UPPER LOBE WITH A QUESTIONABLE SMALL CAVITY

FIG. 7. SAME CHILD AS SHOWN IN FIGURE 6

Plates taken nine months later show definite fibrosis of the lesion with no evidence of cavitation.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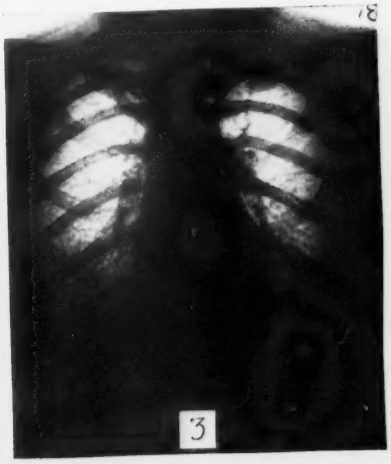
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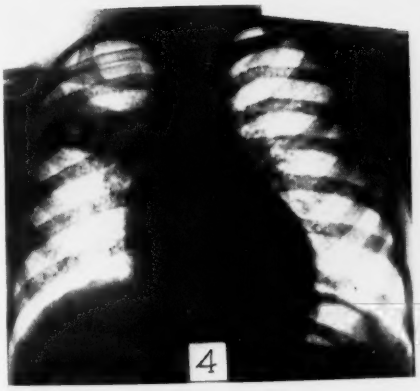
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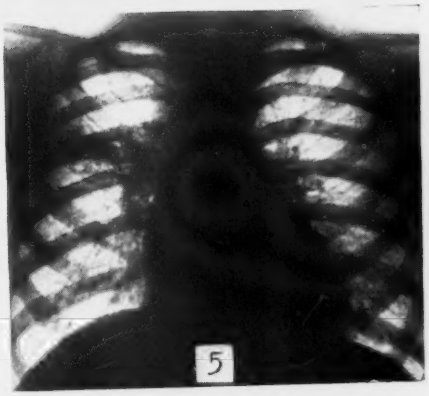
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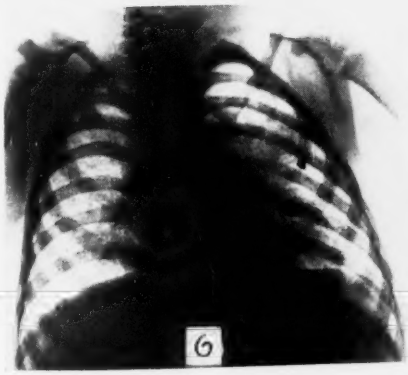
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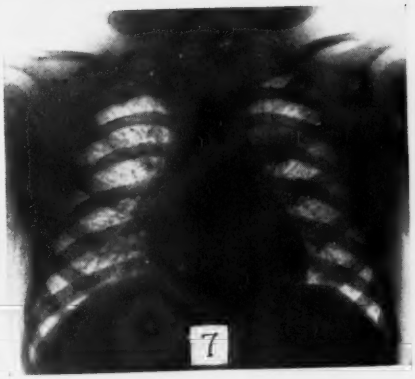
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STUDIES ON TUBERCULOSIS IN INFANCY AND CHILDHOOD[1]

IX. THE INCIDENCE OF PHYSICAL DEFECTS AND NON-TUBERCULOUS DISEASE AMONG 2,000 CHILDREN EXAMINED FOR TUBERCULOSIS[2]

EDMOND NELSON AND J. A. MYERS

Children examined for tuberculosis in dispensaries frequently present many physical defects due to nontuberculous conditions, some of which cause symptoms so closely simulating those of tuberculosis as to render diagnosis difficult. Inasmuch as the dispensary case is usually available for study only a short time, the examiner finds it necessary to quickly make observations on the more common nontuberculous conditions, as well as the tuberculous conditions, and to give them the proper place in the evaluation of the data.

We have tabulated from the records of 2,000 children examined for tuberculosis in the out-patient department of the Lymanhurst School for Tuberculous Children the outstanding physical defects which may be observed in any dispensary for tuberculosis in childhood. Charts 1 and 2 show that deformities, such as Harrison's grove and pigeon breast, were recorded in only 2.6 per cent of the entire group. Although these deformities cause no symptoms and have no relation to tuberculosis, they usually indicate the existence of obstruction in the upper respiratory tract or rachitis in early life. In only 1.4 per cent of this group of cases were significant heart murmurs elicited. Definite thyroid gland enlargement was found in 4.1 per cent. In chart 2 it will be seen that the incidence of thyroid enlargement is very low during the first five years of life. After five years it increases, until it reaches almost 8 per cent at the age of fifteen years. In 1925 Stewart (1) reported the results of a study of the

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[2] This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

thyroid gland in 1,906 Minneapolis school children, ranging in age from birth to eighteen years. He summarizes his work as follows:

The percentage of thyroid glands classed as non-palpable is definitely lower at birth than at any subsequent period during the first two years of life. After

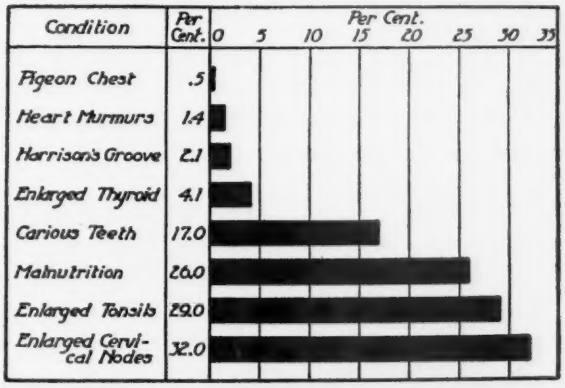

CHART 1. Shows the percentage of children found to possess various abnormal conditions

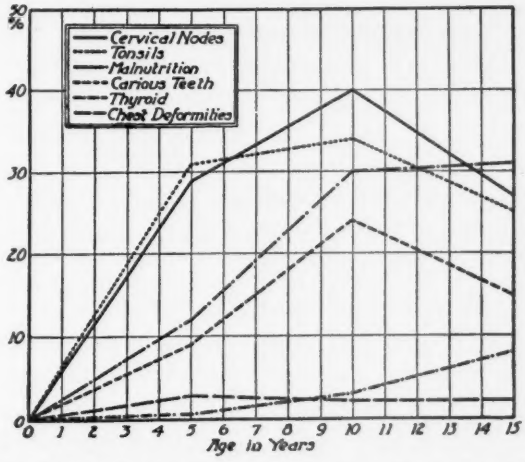

CHART 2. Shows graphically the percentage of various abnormal conditions at different ages of life.

the third to sixth year of age this group of undoubtedly normal thyroids progressively decreases, reaching a minimum percentage incidence for each sex about the age of puberty. Subsequently these non-palpable glands are found with increasing frequency among the boys, but continue to be rarely present among the girls at least until the eighteenth year.

The percentage of very small thyroid glands fluctuates considerably during childhood, but shows no general trend with increasing age.

Slight and considerable enlargements are more prevalent at birth than at other periods during infancy. After the third year these types of enlargement increased in frequency, reaching a maximum about the age of puberty. The considerable enlargement is apparently more persistent among the girls after this period than among the boys.

At no period of life was great enlargement of the thyroid gland as prevalent as hypertrophies of lesser degree. This type of enlargement is very occasionally found in infancy, and subsequently its occurrence is limited practically to girls about the time of puberty or later.

Of our group of children, 17 per cent were found to have teeth in bad condition. The incidence of carious teeth increases until it is about 24 per cent at the age of ten years. From this age it decreases, so as to reach approximately 15 per cent at the age of fifteen years.

Malnutrition was observed in 26 per cent of the children of this group. It increases rather rapidly until the age of ten years, when it is 30 per cent. Then it increases very slowly to slightly more than 31 per cent at the age of fifteen years. Three outstanding causes of malnutrition in children are poverty, ignorance and disease. There is no doubt that poverty plays some part in this group; however, in the city of Minneapolis there is a relatively small indigent population. We are convinced that ignorance of food values and of the needs of the child's body on the part of the parents is responsible for more of our cases of malnutrition than poverty. There is no doubt that disease plays a considerable rôle in our group of malnourished children, since many of them presented foci of infection about the teeth and tonsils.

Enlarged and diseased tonsils were observed in 29 per cent of our group of children. The incidence increases rapidly until the age of five years, when it is approximately 31 per cent. The increase then becomes more gradual, until the incidence is about 34 per cent at the age of ten years. Here a decrease begins, and continues until the incidence is about 25 per cent at the age of fifteen years. No attempt was made to determine the microörganism causing the infection in any case. It has been shown that the primary tuberculous focus may occur in the tonsils. Indeed, studies on large groups of cases have proved that tonsils become tuberculous in from 1 to 8 per cent of the cases studied. Krause (2) calls attention to the fact that tonsils and adenoids are found to be tuberculous in about 5 per cent of a good-sized group of cases well studied. When manifest

tuberculosis is present in other parts of the body we know that the incidence of tonsil involvement is considerably higher than the above figures.

Enlarged cervical lymph nodes were present in 32 per cent of our group of children. Marked enlargements were seen in only a few cases, but the remainder were sufficiently enlarged to be very evident on palpation. In chart 2 one observes that an incidence of 40 per cent is reached at the age of ten years, but that from here the incidence decreases to about 27 per cent at the age of fifteen years. One also observes considerable similarity between this curve and the curves representing carious teeth and enlarged tonsils. This is what one might expect, inasmuch as the cervical lymph nodes receive lymph from the regions of the teeth and tonsils. Here again we have made no attempt to determine the infecting microorganism. This subject is being reserved for a more detailed study. Obviously, there are many causes of enlargement of the cervical lymph nodes in childhood, not the least of which is tuberculosis. Krause (2) has pointed out the fact that cervical lymphadenitis is the most frequent manifestation of clinical tuberculosis between the ages of three and ten years. Some are inclined to believe that tuberculosis of the cervical lymph nodes always causes huge swellings and finally terminates in suppuration. This is not true of all cases; indeed tubercle bacilli may be recovered from lymph nodes that have not been suspected. In writing of tuberculosis of cervical lymph nodes Calmette (3) says:

> Cervical gland tuberculosis is above all a disease of childhood, the period when the child puts its hands to everything (*tuberculose de touche à tout*), appearing in subjects whose lymphatic system is already more resistant than that of young infants. It is the evidence and the result of a neighboring local infection, which may be of the ocular, nasal, buccal or pharyngeal mucosa, or, probably more commonly, of the tonsils. At times the glands have simply retained in their stroma meshes a few bacilli which have been phagocytized by the leucocytes and absorbed through the sub-mucous lymphatic network. It is a primary infection whose intensity and gravity are in proportion to the number and virulence of the bacterial elements. Again the bacilli gain entrance through a small wound or by virtue of a local infection by pyogenic microörganisms (rhinitis, otitis, pharyngitis, tonsillitis, gingivitis, adenoids, etc.).
>
> Tuberculous infection of the cervical glands is generally followed by their more or less rapid engorgement. The glands are hard, movable, and only slightly painful. Among them there is always one much larger than the others of the same group. The lesion within it may remain shut off and inactive for months, later to retrogress and gradually disappear; or again it may progress toward caseation.

Although a routine study of the nasal accessory sinuses was not made in this group of cases, enough sinus examinations were made to convince us that such examinations should become routine. The symptomatology in minimal tuberculosis and sinusitis may be so nearly the same as often to make differential diagnosis difficult. We should like to call attention to two such cases. These children were referred by physicians who had made diagnoses of tuberculosis. A period of observation in bed, however, revealed no evidence of tuberculosis or even tuberculous disease, and under the rest treatment their symptoms disappeared. After a few weeks of study they were discharged as nontuberculous. In the course of a few weeks, however, their physicians observed recurrence of the former symptoms and returned them with diagnoses of tuberculosis. Observation again revealed no evidence of tuberculosis, but careful study, including X-ray of the sinuses which for some unexplainable reason was not made during the first period of observation, revealed definite involvement of the maxillary sinuses. Proper treatment of the sinuses relieved the patients of all symptoms, and there has been no recurrence. A number of other similar cases might be cited. Indeed, sinus involvement is so common and may lead to so much confusion in diagnosis, that we have become convinced that routine X-ray plates of the sinuses are almost as important as routine X-ray plates of the chest in the detection of obscure conditions, from which so many of the children applying to the Lymanhurst Out-patient Department are suffering.

It is a well-known fact that tuberculosis involves the tonsils and cervical lymph nodes in many cases, but there are many other cases with nontuberculous disease of these parts. The differentiation between tuberculous and nontuberculous disease is not always easy. It is also a well-known fact that hyperthyroidism may cause symptoms which very closely simulate those of tuberculosis. The differentiation between these conditions may also require considerable time. Attention has also been called to the danger of crediting tuberculosis with symptoms from ordinary infected sinuses.

The physician assumes a tremendous responsibility when he renders a diagnosis of tuberculosis. Perhaps he assumes an equal responsibility when he states that tuberculosis does not exist. Because of the physician's responsibility, and because of so many difficulties in differentiating between mild tuberculous disease and many nontuberculous conditions in childhood, our group of cases has convinced us that the private physician or the dispensary physician had best withhold diagnosis in all

cases in which any question arises, until a detailed and complete examination is made and a satisfactory period of observation in a hospital or the home is completed, and all findings are carefully analyzed.

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STUDIES ON TUBERCULOSIS IN INFANCY AND CHILDHOOD[1]

X. TUBERCULOUS INFECTION AMONG MINNEAPOLIS SCHOOL CHILDREN AS REVEALED BY THE INTRACUTANEOUS TEST[2]

F. E. HARRINGTON AND J. A. MYERS

In 1907 Pirquet (1) announced the discovery of a cutaneous tuberculin reaction, which has come to be regarded as a very reliable procedure for the detection of tuberculous infection. One year later Mantoux (2) introduced the intracutaneous tuberculin test. Since that time several modifications of these tests have been devised, but none has approached either of them in popularity. There has been much discussion regarding the relative merits of the Pirquet and the Mantoux tests, but within recent years the Mantoux test has so gained in favor with physicians as now to be fairly generally regarded as the better of the two tests. For example, Brinchmann (3), Reiss (4), Cunningham and Ratcliffe (5), Wahl and Gerstenberger (6), Hamburger (7), and Veeder and Johnson (8), do not find cases positive to the Pirquet test and negative to the Mantoux test, but they do find cases negative to the Pirquet test and positive to the Mantoux test. Indeed, some workers have reported the intracutaneous test as much as 20 to 30 per cent more delicate than the cutaneous test. It appears, therefore, that the Mantoux test is somewhat more reliable than the Pirquet test.

The incidence of tuberculous infection among school children, as revealed by tuberculin tests, varies a great deal according to reports made from different parts of the world. In an industrial school near Edinburgh, McNeil (9) found that 60 per cent of the boys reacted positively, while not far away in a similar school only 14 per cent reacted positively.

In table 1 are arranged the percentages of positive tuberculin reactions

[1] From the Lymanhurst School for Tuberculous Children, Minneapolis, and the Departments of Preventive Medicine and Internal Medicine, University of Minnesota.

[2] This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

at various years of school age as reported by a few workers. Here one sees in one part of the world more than 90 per cent of the children reacting positively before reaching the age of fourteen years, while in other parts the percentages reported are considerably lower, even reaching the low mark of 13 per cent in one rural district.

Our work was undertaken to determine the incidence of tuberculous infection among a group of Minneapolis school-age children. Permission was received to apply tuberculin tests to children in different parts of the city. The intracutaneous test was employed, beginning with one minim

TABLE 1

Percentages positive to tuberculin test according to different authors

AGE	VIENNA	VIENNA	GERMANY	SASKATCHEWAN	NEW YORK	THE HAGUE	ST. LOUIS	GERMANY	RURAL MINNESOTA
	Hamburger and Monti (16)	Pirquet (1)	Barchetti (17)	Ferguson (18)	Sill (19)	Furstner-Risselada (20)	Veeder and Johnson (8)	Bruning (21)	Slater (22)
years									
6	61			44.4		20	40	36.8	10
7	73	64	58		10.25	20		29.0	6
8	71				15.95	28	44	40.9	10
9	85					32		42.1	11
10	93	80	71	57.4	47.62	43	40	46.4	11
11	95					30		28.6	9
12	94				50.0	41	48	35.3	12
13	94					50		46.2	12
14									13
15									7

of a 1 to 1000 solution of tuberculin. About one week later those who reacted negatively to the first test received one minim of a 1 to 100 solution. Although Mantoux advocated beginning with a solution of 1 to 5000, and some workers begin with 1 to 10,000, we observed no severe reactions in our group of cases. Some workers have found that a few cases giving no reaction to a 1 to 100 solution will react positively to a 1 to 10 solution. We did not use tuberculin stronger than in 1 to 100 dilution. Our group consists of 2,188 children. It will be seen in table 2 that 776 children reacted positively to a tuberculin dilution of 1 to 1000. There were 229 other children who reacted negatively to 1 to 1000, but positively to a 1 to 100 dilution. In table 2 and chart 1, it will be seen that,

except for the sixth and the fifteenth years, the incidence of infection is somewhat higher among the boys than among the girls. However, the

TABLE 2

Tuberculin tests among school children of Minneapolis

AGE	SEX	NUMBER TESTED	POSITIVE 1 TO 1000	NEGATIVE 1 TO 1000 POSITIVE 1 TO 100	PER CENT POSITIVE
years					
6	Male	59	4	5	15.25
	Female	66	10	7	25.75
7	Male	82	15	8	28.04
	Female	90	17	7	26.66
8	Male	125	39	13	41.60
	Female	147	45	9	36.37
9	Male	149	45	21	44.29
	Female	167	54	10	38.32
10	Male	151	67	15	54.30
	Female	143	53	14	46.85
11	Male	137	62	16	56.93
	Female	137	63	7	53.84
12	Male	105	45	24	65.71
	Female	141	60	18	55.31
13	Male	99	51	8	59.59
	Female	132	65	11	57.57
14	Male	67	35	14	73.13
	Female	48	20	11	64.59
15	Male	43	14	7	48.84
	Female	30	12	4	53.33
Total number tested	Male	1017	377	131	48.76
	Female	1101	399	98	45.89
		2118	776	229	

Total number positive = 1005.
Per cent positive of total number tested = 47.33.

averages for the entire group show 48.76 per cent for the boys and 45.89 per cent for the girls. As age increases, the incidence of infection, as

indicated by the intracutaneous reaction increases, with a few exceptions. It is quite probable that the irregularities in the curves (chart 1) would smooth out considerably if an equal number of children were included for each age and much larger numbers of children had been tested.

One may ask whether all the positive reactions were due to living tubercle bacilli. Petroff and Zinsser (10), working with guinea pigs, have been able to produce hypersensitiveness to tuberculin without infection. From their work it is known that when tubercle bacilli are killed by heat and inoculated into the bodies of guinea pigs the animals

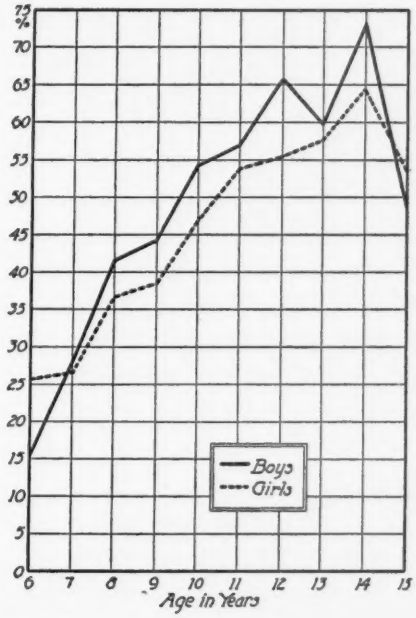

CHART 1. SHOWS THE INCIDENCE OF TUBERCULOUS INFECTION AS REVEALED BY THE MANTOUX TEST AMONG BOYS AND GIRLS AT DIFFERENT AGES

react to tuberculin skin tests in the same manner as tuberculous animals react. Although the effect is transitory it is definite, and may be produced after the bacilli have been heated to 100°C. Is it possible, then, that in a city with a pasteurization ordinance in effect on 96 per cent of the milk supply, there may be enough dead tubercle bacilli in the milk to produce hypersensitiveness to tuberculin in children? Since most communities are supplied by several milk companies it is not likely that there would be uniformity of distribution of tubercle bacilli. Again the

children in some families take large quantities of milk, while those in other families take little or none. From the work of Petroff and Zinsser, the question arises as to whether the ingestion of dead tubercle bacilli in pasteurized milk may account for hypersensitiveness to tuberculin in children. This, in turn, raises the question as to whether dead tubercle bacilli are absorbed by the digestive tract and, if at all, whether they are absorbed in sufficient numbers to produce hypersensitiveness to tuberculin. From work done in the past it is questionable whether they are absorbed at all; therefore, we are inclined to believe that the ingestion of dead tubercle bacilli would not account for a large percentage of our cases reacting positively to tuberculin. Wang (11) has pointed out that in children fed on raw cow's milk the incidence of tuberculous infection as revealed by the tuberculin test is much higher than in children fed on boiled cow's milk.

In our group of cases no attempt was made to determine which type of tubercle bacillus caused the hypersensitiveness to tuberculin.

Until recent times it was generally believed that, once a person becomes infected with tubercle bacilli, the hypersentiveness to tuberculin persists throughout life. Therefore, it was thought possible, in any community or in any group of people, with the application to all of a tuberculin skin test, to determine with a high degree of accuracy the percentage who had ever been infected.

In 1922 Krause (12) said

> No one has yet kept careful records from infancy to and through adolescence, of the ups and downs, the appearance, disappearance and reappearance, of the Pirquet reaction, that index to infection, in only ten of the millions of infected children. It may be that for longer or shorter periods we would find that a large proportion would exhibit nonreactivity, and therefore noninfection, where reaction and infection had been shown before; and further that many of these would later again give the test of infection,—in their case, reinfection.

In 1924 Austrian (13) reported a group of children, some of whom had been observed since 1915. In 1920 he found 10 children with negative tuberculin reactions who had positive reactions in 1915–1916. In 1923 these children were retested and 7 still were negative. Among the other children who had reacted positively in 1920, three were found to have become negative in 1923. Inasmuch as there was no condition present in any of these 10 children to account for the loss of hypersensitiveness to tuberculin, it appeared that they probably represent a group in whom

tuberculous infection so dies out as to leave no demonstrable evidence of its former existence. Austrian also pointed out that in some of his cases tested at rather frequent intervals there appeared a variation in intensity of the tuberculin reactions. This raised the question as to whether the changes in intensity were due to changes in the primary infections or to new infections.

In 1919 Krause (14) reported a case of multiple tuberculosis that first came under observation in 1909. At the time of the first observation this boy was nearly four years old. In 1917 the disease became arrested and although this child had been very sensitive to tuberculin previously he now (1917) reacted negatively to the Pirquet test. In 1925 Krause (15) made a further report on this case in which he says

> This boy has now become a young man of twenty. I see him once a year, when he is thoroughly examined, roentgenographs of his chest are taken, and skin tests (Pirquet) made. For eight successive years (since 1918) he has remained negative to the Pirquet test. Needless to say, also, he has kept in perfect health and worked (as a clothes-presser) without interruption. Except for the old scars of his numerous operations he presents no evidence of tuberculosis anywhere.

Again Krause says: "The conclusion is compelling that if such extensive infection can be done away with and such great hypersensitiveness can vanish, the more ordinary condition of less or slight infection and hypersensitiveness is frequently disappearing."

In the light of the available evidence that tuberculous infections die out, we have come to realize the impropriety of believing that all persons reacting negatively to tuberculin have never been infected. Therefore we are not able to determine by a tuberculin test how many children in a given school or persons in a given community have been infected as we formerly believed we were. The percentage of infections that die out so completely as to leave no evidence of their previous existence, even by tuberculin testing, can be determined only by extensive studies and observations of the same groups of children over long periods of time.

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STUDIES ON TUBERCULOSIS IN INFANCY AND CHILDHOOD[1]

XI. SERIAL EXAMINATIONS OF INFANTS SHOWING POSITIVE TUBERCULIN SKIN REACTIONS WHILE UNDER TWO YEARS OF AGE[2]

H. F. WAHLQUIST AND J. A. MYERS

Until recently it was believed that tuberculous infection in children under two years of age would almost invariably result fatally. However natural this supposition might be under certain conditions, in which repeated massive doses of infection with the tubercle bacilli are received under ordinary conditions of life, and in a large number of cases too in which the infant is subject to constant exposure, the facts established do not bear out this assumption.

Since Pirquet (1) announced the discovery of his test, the opinion of those in touch with the situation has gradually changed, and the prognosis of infants infected with tuberculosis is not so grave as it was formerly thought to be.

However, in searching through the literature, we find the mortality statistics still high. The actual mortality in a series of 23 cases, studied by Reuben and Smith (2) which had become infected during the first year of life was 53 per cent. Oswald (3) cites a mortality of 59.15 per cent in pulmonary and bronchial-node tuberculosis.

In 1917 Hempelmann (4), questioning the soundness of the pessimistic view regarding infantile tuberculosis, wrote as follows, "Actual studies of the fate of children infected with tuberculosis in infancy are extremely few." He then presented his own observations on the outcome of pulmonary tuberculosis in 130 infants under two years of age. His average mortality was 78.7 per cent during the first year of life, and 57.4 per cent between the ages of one and two years.

In 1925 Lemaire (5) reported the results obtained from a study of 100

[1] From the Lymanhurst School for Tuberculous Children, Minneapolis, and the Departments of Internal Medicine and Preventive Medicine, University of Minnesota.

[2] This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

tuberculous children less than two and one-half years old, whom he observed over periods varying from three months to more than two years. The mortality in this entire group was 24 per cent. However, among those infected during the first year of life the mortality was 57 per cent. It is interesting to note that family contagion existed among 95 per cent of those who died, and among only 77.6 per cent of those who survived. It was shown further that among 67 children who were separated from their parents, 4.5 per cent died, while among 33 children who were not separated from their parents 63.6 per cent died.

McLean and Jeidell (6), in a group of 147 infants with positive tuberculin tests under one year of age, found that 75 died in a hospital and 7 had tuberculous meningitis when removed from a hospital. Of their entire group 54 did not develop definite tuberculous disease. In a group of 151 children with positive tuberculin tests between one and two years of age the mortality was 37.7 per cent.

For the most part the reports that have been made in the past were on groups of children who were ill enough to require the services of physicians. Many of them had not only tuberculous infection but also tuberculous disease when first seen. No doubt this accounts in considerable part for the high mortality that has been reported so often. The careful studies of Reuben and Smith (2), Hempelmann (4), Krause (7), and others have shown that even when tuberculous disease exists in the infant the prognosis may be good in a fairly high percentage of the cases, and that in some instances complete healing occurs. They point out further that, since it is true that some infants recover from severe tuberculous disease, perhaps many overcome simple infections without ever presenting any manifestations of disease. Indeed Reuben and Smith state that they have had occasion to observe 6 cases which, if it were not for the presence of positive Pirquet reactions, the tuberculosis would have been entirely missed. All of these cases were alive and well at the time the report was made.

Krause (7) recently said:

> We may be certain, for instance, that the number of infected infants is several times that of those ill with tuberculosis. Infection tests, performed thus far, indicate that, on the average, about 10 per cent of the general run of dispensary infants of one year of age react positively. Of course, the number dead or ill from tuberculosis at this age is nowhere near this proportion; and these newer facts of the evidence of infection must surely make us revise our older ideas of the extreme gravity of tuberculous infection, as such, for young infants.

He continues by saying that "The more I see of tuberculosis in infants and the more I confirm diagnosis by the aid of new methods, the more tuberculous infants I find who run along with comparatively little illness and withstand their infection well." His experience in the last few years has convinced him that (1) many infants become infected and never fall ill with tuberculosis, (2) in many there are symptoms, but so slight and indefinite, as to have their real significance unappreciated in ordinary practice, and (3) many even of those who exhibit symptoms of illness due to tuberculosis make good recoveries.

Krause further emphasized the fact that "During 1915 to 1920 the tuberculosis death rate for male infants, from birth to four years, in New York City was 150 per 100,000 alive. The infection incidence was surely as high as 10 per cent or 10,000 per 100,000. On this basis, it would appear that only one of every 66 infected male infants died from tuberculosis."

It was these facts that prompted the present survey at the Lymanhurst Out-patient Department, where 71 cases of children up to two years of age have had tuberculous infection revealed by the Pirquet test.

The work was begun more than two years ago, when a mother and father brought their baby boy of six months for an examination. The parents were well-to-do and intelligent, but the mother was crying. She stated that she had just been told that their baby would die within the next six months. A little questioning revealed the fact that the parents had taken the baby to a physician who, knowing that a near relative had recently died of tuberculosis, made no examination except a Pirquet test. This test proved positive and, without further examination, the physician told the parents that their baby could not live to its first birthday. This child had never been ill a day in its life and from every appearance was in perfect health, and at the present time he is a well-developed child having never manifested any evidence of tuberculosis.

In conducting this study, every effort was used to obtain uniform results by the employment of one simple technique. Koch's Old Tuberculin, human type, was used, and three scarifications were made approximately one inch apart; to the upper and lower ones was applied the tuberculin, while the centre one was used as a control. In an occasional instance the control showed an area of erythema, probably due to lymphatic drainage or trauma. In no instance, however, was a test considered positive unless both the upper and lower areas demonstrated

a definite reaction, as evidenced by a red areola and induration at the point of scarification. Two scarifiers exactly alike were used; one for the tuberculin and the other for the control, thus avoiding the possibility of having tuberculin deposited on the control area. The tests were interpreted 48 hours later by the nurse who assisted at the time they were applied.

In grouping these cases under various headings we found a definite history of exposure in 95.7 per cent of the total series. Exposures were equally divided between mothers and fathers in 72.2 per cent, 11.2 per cent were exposed to tuberculous brothers and sisters, while 15.5 per cent gave a history of exposure to several sources of infection (table 1). The greater amount of tuberculosis in parents of this group of children is, of course, due to the fact that at any tuberculosis clinic the children

TABLE 1

Infants at Lymanhurst Clinic reacting positively to tuberculin

AGE	NUMBER OF CASES	MALES	FEMALES	EXPOSED TO MOTHER	EXPOSED TO FATHER	EXPOSED TO BROTHER OR SISTER	SEVERAL SOURCES OF EXPOSURE	NEGATIVE HISTORY OF EXPOSURE	POSITIVE HISTORY OF EXPOSURE
Birth to 6 months.....	9	4	5	4	5	0	0	0	9
6 to 12 months.....	12	5	7	3	3	3	2	1	11
12 to 18 months.....	13	8	5	3	3	2	3	2	11
18 to 24 months.....	37	20	17	16	15	3	3	0	37
Total.....	71	37	34	26	26	8	8	3	68
Percentage.....		52.1	47.9	36.6	36.6	11.2	11.2	4.3	95.7

represent largely the offspring of tuberculous adults. This is an important point, and if we can reduce the amount of contact with tuberculous cases there is no doubt but that infection in children can be reduced. If contact takes place through one of the members of the family, the chances are that the infection will be greater because of the intimate and frequent exposure. Falk (8) made a study of 90 children of parents with positive sputum. He found that 100 per cent of the children were infected when the parent's disease was fatal. Bernard and Debré (9) emphasize the importance of separating the infant from the tuberculous parent even if already infected, for it is the prolonged, repeated infections that determine the severe tuberculosis in infants. The authors assert

that if an infant does not die within a month of separation, the disease will probably not prove fatal. In the Laennec Hospital for tuberculous mothers, the infants are taken away at once. If after repeated tuberculin tests, they are found free from tuberculosis, they are placed in private homes. If they are already infected, they are kept under observation to determine the degree of infection.

Drolet (10), on the other hand, showed that the results of tuberculin reactions in children from tuberculous parents as compared with those in children of nontuberculous parents were practically alike. It must be remembered, however, that in our group in the majority of cases the child was brought to the clinic because of tuberculosis in the home, and we had little opportunity to study cases giving negative histories of exposure within the two-year age limit.

TABLE 2

Findings in Lymanhurst Clinic infants with tuberculous infection

AGE	NUMBER OF CASES	POSITIVE PHYSICAL FINDINGS	NEGATIVE PHYSICAL FINDINGS	SYMPTOMS	NUMBER OF CASES DIED	CAUSE OF DEATH	NUMBER OF CASES IN INSTITUTIONS	POSITIVE X-RAY FINDINGS
Birth to 6 months..	9	4	5	2	0		2	1
6 to 12 months....	12	6	6	5	2	Pulmonary tuberculosis. Tuberculous meningitis	2	6
12 to 18 months....	13	5	8—	3	1	Tuberculous meningitis	0	6
18 to 24 months....	37	17	20	11	3	Pulmonary tuberculosis	4	16
Total.....	71	32	39	21	6		8	29
Percentage.....		46.5	53.5	30	8.4		11.2	40.8

Lange (11) has observed 20 infants who survived tuberculosis, and who were only subjected to infection by their severely tuberculous parents for a short time, so that superinfection was excluded. The danger to the infant therefore is ascribed to superinfection.

Some physical sign, such as interscapular dulness, was present in 46.5 per cent, and negative in 53.5 per cent of cases in our series (table 2). Constitutional signs and symptoms, particularly fatigue, loss of weight or failure to gain weight, weakness and fever, were present in 30 per cent. Roentgenograms of the chest showed changes particularly in the region of the hilum in 40.8 per cent of the observations made in this series. These figures show the great diagnostic value of roentgenograms in tuberculosis of the first two years of life.

The most striking observation in the whole study is the low rate of mortality, which did not exceed 8.4 per cent, due to tuberculosis. Of these, 2 cases died between the ages of six and twelve months, one case between twelve and eighteen months, and 3 between eighteen and twenty-four months. The cause of death was tuberculous meningitis in two instances, while four died from pulmonary tuberculosis; 11.2 per cent are now being treated.

These mortality figures are indeed startling, but it must be remembered that we are speaking of cases with infection, as evidenced by the Pirquet test, and not limiting ourselves to obvious cases of tuberculous disease. The question of hilum lymph-node involvement, cough, fever, etc., was secondary in consideration to the skin test. Of course, many of these cases would have been entirely missed if it were not for the presence of positive tuberculin tests, and, as previously stated, the majority of them were brought to the clinic, not because of symptoms, but mainly because of exposure.

What the outcome of these cases will be is difficult to say, but no effort will be spared in endeavoring to reëxamine them, as well as new cases that are being added to our group, at least once during each six months' period.

CONCLUSIONS

1. The prognosis of simple tuberculous infection in infants is not so grave as it was formerly thought to be.

2. The tuberculin skin test is an indispensable aid in diagnosing early tuberculosis.

3. A positive tuberculin test up to two years of age does not necessarily mean an active tuberculous process; it merely indicates tuberculous infection.

4. There was a definite history of family exposure in 95.7 per cent of the cases. Therefore, the necessity of early separation of infants from tuberculous individuals is clear.

5. The greater proportion of infants who become infected with tuberculosis in our series have not become ill with tuberculous disease.

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STUDIES ON TUBERCULOSIS IN INFANCY AND CHILDHOOD

XII. A STUDY OF THE LUNG HILUM IN A GROUP OF CHILDREN EXAMINED FOR TUBERCULOSIS[1,2]

H. A. BURNS AND J. A. MYERS

The infection from the tubercle bacillus tends, through the formation of tubercles, to become a focal infection. This tendency remains true, with but few exceptions, regardless of the extent or progress of the disease. The biology of the tuberculous invasion has received much attention since the skin reactions and the X-ray have made it possible to study, with considerable accuracy, the early manifestations of tuberculosis in the child. Ghon demonstrated primary foci in the lungs, and traced tuberculous bronchial lymph nodes to an earlier and older primary focus. Such a focus is seen in figure 1. Pirquet classifies tuberculosis into three stages: (1) The primary, which is synonomous with the primary focus as demonstrated by Ghon; (2) a secondary state, which is the lymphatic manifestation of the disease, the juvenile type, and (3) the tertiary or third stage of the invasion, which is the adult type of infection. Chadwick, Dunham, and others have divided tuberculosis into three classes, depending largely upon the age-group, into infantile, juvenile and adult types. The difference in these two classifications depends upon the interpretation of the infantile type. It has long been held that infection prior to the second year of life would end fatally, and the high mortality rate during the first two years of life gave rise to this clinical classification, which is pathologically a combined first, second and third stages, occurring in certain infants who suffered an overwhelming "dose" of bacilli at a time when the tissues were unable to react sufficiently to localize the infecting agent in the lymph nodes.

The infantile type of tuberculosis usually occurs some time before the

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end of the first year of life. It develops quickly as an acute infection, terminating frequently in a meningitis or pneumonia. Little or no tendency is shown by the disease to localize. Usually, in the second year of life the individual's immunity increases with the power of the tissues to react, localizing the bacilli in the adjacent lymph nodes. From the second to the twelfth or fourteenth year, tuberculosis remains largely a disease of the lymphatics. It is of great importance in the study of the epidemiology of tuberculosis to know that the age-group from two to twelve or fourteen years contains a relatively larger number of infected persons than either of the other two groups, yet the death-rate is negligible in this group, as compared to the deaths during the first two years and following the fourteenth year of life.

In the registration area of the United States during 1922 there were 88,385 tuberculosis deaths, 3,012 of which occurred during the first two years of life, an average of 1,506 deaths each year. From two to fourteen years there occurred 4,463 tuberculosis deaths, an average of 343 deaths per year. From fifteen to fifty-five years of life, there occurred 66,350 tuberculosis deaths, an average of 1,658 deaths per year for forty years.

Prior to the development of the X-ray and the skin reactions, tuberculosis was recognized clinically in its secondary phase only when the superficial lymphatics became involved. The entire problem of tuberculosis diagnosis, treatment and control was originally limited to the third stage of the disease. The diagnosis of the disease concerned itself with its final stage, while prophylaxis and treatment of the earlier manifestations of the tuberculous invasion remained in obscurity until revealed through the development of the X-ray and the skin reactions. These aids in the diagnosis of the disease have demonstrated the fact that tuberculosis has an epidemiology quite its own. The collection and study of data, accumulated as a result of the use of present-day equipment and in the light of our present knowledge, have provided the physician with most valuable information, which promises, when finally evaluated, to guide us to principles of prophylaxis and control just as applicable in the control of tuberculosis as in other infectious and contagious diseases.

A survey of the literature leaves little to conjecture in tracing the infection from the point of entrance until the time when the classical pathology of tuberculosis has developed a classical symptomatology. The significance of the skin reaction in the early diagnosis of tuberculous infection, as well as the tuberculization of childhood, is already an

accepted procedure confirmed by research, autopsy findings, and clinical experience.

Lampson (1) in 1913 made a study of the spread of tuberculosis in families in Minnesota. He visited 36 tuberculized families among whose 161 members there had recently occurred 9 deaths. In these families

111 children were under fourteen years of age.
37 adults were active cases at the time of the investigation.
108 showed positive Pirquet reactions.
53 showed negative Pirquet reactions.
135 showed evidence of tuberculous infection, including the 37 active cases.

The skin test has taken its place as an important procedure in the study of tuberculosis. The interpretation of the chest plate of the child still requires standardization in its interpretation. Hawes and Friedman (2) state that the interpretation of mediastinal-node enlargement by both the clinician and roentgenologist is in a chaotic state. The etiology of mediastinal lymphadenitis may be traced to various causes, among which are the acute respiratory infections, for which the lymph nodes at the hilum become a sensitive register, reacting quickly to the irritating element, which has become localized in the area whose lymphatics drain into the reacting lymph nodes. Krause (3) and Calmette (4) have pointed out the fact that in experimental animals the bronchial lymph nodes may become involved before any involvement is found in the lung parenchyma. If a tuberculous process develops in the lung, whether it be a primary focus in a child or adult type of tuberculosis, the region of the hilum is quick to become involved with lesions of secondary localization. These secondary lesions are believed to be caused by bacilli, which escape from the parenchymal lesions. In such cases serial studies of the lung-hilum region may be enlightening. Just as we know that not all enlargements of the cervical, inguinal and axillary lymph nodes are due to tuberculous infection, so enlargement of the lymphatics in the hilum region may also be due to other causes. Krause (5) says, "There may always be legitimate grounds for dispute as to the significance, particularly as regards etiology, of enlarged and widened mediastinal shadows in children who are free from symptoms of pulmonary disease." Fleischner (6) states that simple bronchial lymphadenitis is a distinct clinical entity in childhood, classifying these forms under acute, subacute, and chronic. He concludes, "When one considers the great incidence of infection to which bronchial lymphadenitis is secondary, the general conclusion can be reached that this type of disease, in contrast to tuber-

culosis, is the most common disease of the bronchial lymph nodes." Densities in the lung field tend to disappear rapidly when the infecting agent subsides. Adenopathies in any part of the body develop in accordance with Parrot's law (7), and the elimination of the etiological factors, serial plates symptoms and the skin tests all make it possible to arrive at a diagnosis with a minimum of error.

Gähwyler (8) reports 7 cases that had physical signs, X-ray findings, and even symptoms, very suggestive of tuberculosis of the bronchial lymph nodes, in which careful observations, including repeatedly negative tuberculin tests over a period of years, have proved to his satisfaction that they were nontuberculous. His observations on the evidence of calcification have convinced him that it is impossible by means of the X-ray to differentiate between calcifications caused by tuberculous and nontuberculous conditions.

Kuss (9), followed by Ghon (10), whose work was still later confirmed by Canti (11), indicates the point of entrance in the lung by the findings of a primary focus and an enlargement of the adjacent bronchial lymph nodes. The primary focus in the lung is of little clinical significance unless it can be demonstrated. This is only possible through the aid of the X-ray, and then only provided fibrosis or calcification has taken place. While it is true that there are various conditions, which, if present, will cause an adenopathy of tracheobronchial lymph nodes, these are usually of an acute nature, tending to self-limitation and absorption as soon as the infecting agent has stopped draining into the affected nodes. Serial plates showing a persisting enlarged mediastinum (figure 2), the chronicity of which may be further indicated by calcification, is evidence, though not positive proof of tuberculosis. Further confirmation by aid of the skin reaction, history and symptoms have added considerably to the picture, which, clinically interpreted, often means the symptoms accompanying the tuberculization of the child. As only a few present fibrous or calcareous changes at the site of the primary focus, we cannot always demonstrate the primary focus in the stereoscopic plates. However, as the lymph nodes are more prone to calcareous changes in the presence of tuberculous infection than as a result of other toxemias or irritants, the bronchial lymph nodes draining the area of the primary focus will enlarge, and frequently calcify (figure 3), blazing a trail for us in its evolving from a simple localized lymphatic infection to a disease of major importance, involving any or all organs of the body and creating a public health problem, which has challenged our medical knowledge

to combat. This challenge remained uncontested so long as we considered the infection in its third stage to include the entire tuberculosis problem.

The establishment of the tubercle bacillus in the body, successfully forcing the tissue cells to act as host, is determined more by the number of invading microörganisms than by their virulence. Dosage is an important factor, which, while not protecting the host against the invasion, does determine the extent of the lesion and the response of the defensive mechanism of the body against it. In order that bacteria may be taken up by the pulmonary lymphatics it is maintained that there must be trauma of the mucous membranes somewhere along the respiratory tract. Cheeseman and Meltzer (12) in 1898 demonstrated the importance of trauma in preparing a point of entry for bacteria. Winternitz (13) has elaborated this theory, and added much to our knowledge concerning the defensive mechanism of the body against infection through the respiratory tract. In his study of the acute respiratory infections during the influenza epidemic of 1918, Winternitz considered those cases which were complicated by pneumonia to depend upon trauma to the respiratory-tract mucous membranes. Concerning the development of pneumonia as a complication following influenza infection, he concludes "The inhalation of such organisms is without effect unless the respiratory tract has first been irritated or damaged. It is true of course that when the functional capacity of the mechanism is lost pneumonia follows." If the portal of entry for the tubercle bacillus is as dependent upon trauma as has been demonstrated in the case of pneumonia following influenza, then it becomes a disease of childhood, not so much because of age susceptibility, but rather because of greater possibilities of the tubercle bacilli gaining entrance through trauma during the period of childhood. The communicable diseases, most of which are contracted during the early years of life, as well as pulmonary congestions resulting from exposure, create a condition of trauma repeatedly and covering a variable length of time during the first fourteen years of life, making it possible for the tubercle bacilli to pass from the damaged mucous membrane into the pulmonary lymphatics. Tuberculization during the early years of life would seem, in large measure, to be due to the frequent damage to the respiratory tract as a result of these infections of early life.

Waldimiroff (14) says, in discussing the tuberculosis curve, that "it does not indicate an increase or decrease of the disease itself but the measure of resistance against the dosage, for in cultured centres the

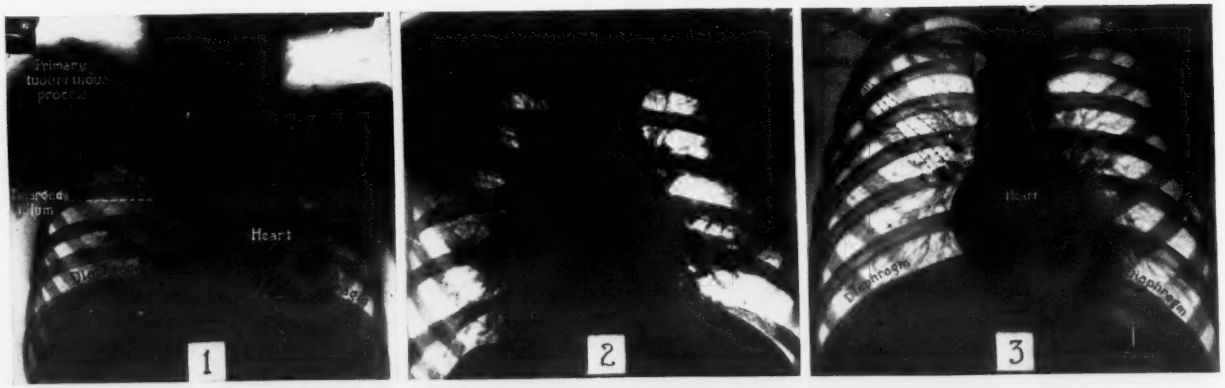

FIG. 1. Roentgenograph of chest of child, to show primary focus in right second interspace with enlarged hilum shadow on same side.

FIG. 2. Roentgenograph of chest of child, to show marked enlargement and calcification of the hilum on each side.

FIG. 3. Roentgenograph of chest of child, to show extensive calcification in the region of the right hilum.

population is considered tuberculized after a certain age." Knopf (15) says that tuberculous disease in childhood is relatively rare, while tuberculous infection is exceedingly frequent.

Chadwick (16) states that tuberculosis should be considered a children's disease. He cites the reasons underlying the neglect in the recognition of tuberculosis in children to be due largely to the fact that we fail to consider the transition of the infection from the lymphatics to lymphoid tissue, while recognizing and attempting the control of the disease in its third and final manifestation. Seventeen per cent of all deaths from tuberculosis occur in the age-group one to nineteen years. This group, as has largely been shown, includes those suffering from the second stage or juvenile type of the disease, which has a relatively low death-rate, yet this death-rate during these early years indicates an important relationship between the second or juvenile stage and the third stage of adult or apical tuberculosis. The process of tuberculization exacts a terrific toll, which is continued to some degree throughout early and middle life. Deaths, with but few exceptions, are caused by an invasion of organs or tissues of the body after the infection has passed the second stage. Death from tuberculosis is a third-stage death. The problem of tuberculosis, its prophylaxis, epidemiology, and control, logically demands our attention not later than the second stage of the disease while it is yet localized in the lymphatics.

Bushnell's opinion (17) is that "cases of manifest tuberculous disease are cases of failure of immunization in a minority of the population." The problem of tuberculosis control centres in the child, particularly the child living under conditions of overcrowding and defective ventilation. These conditions are important, chiefly no doubt because they favor a continuous exposure as soon as an open case of tuberculosis enters the environment. It is not the elimination of tuberculosis as a disease of childhood that concerns the student of tuberculosis, but rather the ability to provide the child with an environment that will minimize the dosage and interrupt the continuity of exposure for any one child. Whether general tuberculization of a population during childhood is a safeguard is an unsettled question. The great majority of the population are infected and eventually immunized by the process, and only a comparatively few become manifest cases of clinical tuberculosis. The control measures sought are not through the management of the manifest cases, but rather reaching the juvenile case and aiding in the prevention of the third-stage development by gaining an arrest while the tuberculous invasion is yet a tracheobronchial lymph-node disease.

A study of 1,412 children examined at the Lymanhurst School has been made in an attempt to add some light to the study of the hilum in childhood and its relation to tuberculous infection. The history of exposure, followed by a positive skin reaction and clinical manifestations of a chronic infection, confirmed further by stereoscopic plates, is sufficient to warrant a diagnosis in the absence of pulmonary symptoms of juvenile tuberculosis.

TABLE 1

Summary of 1412 cards reviewed and classified by age-groups

AGE IN YEARS	TOTAL CASES	EXPOSED		PIRQUET		TOTAL X-RAY	X-RAY NOT TAKEN	HILUM CALCIFIED	BRONCHIAL NODE CALCIFIED	PRIMARY FOCI	HILUM NODES		
		Plus	Minus	Plus	Minus						Moderately enlarged	Greatly enlarged	Normal
0–1	25	22	4	13	1	25	0	1	0	2	1	3	21
1	16	10	5	5	9	14	2	4	0	0	7	0	7
2	41	36	6	13	30	41	0	11	1	2	20	0	20
3	43	27	16	14	29	38	5	19	0	2	28	0	10
4	65	46	21	28	37	54	11	47	1	4	48	0	5
5	71	48	24	33	37	56	16	46	1	12	41	0	15
6	115	59	45	44	65	97	18	68	3	13	80	5	9
7	117	49	68	47	70	81	36	74	9	25	62	1	10
8	144	69	75	65	78	121	23	111	10	26	89	1	10
9	129	54	75	64	63	107	22	96	2	28	82	5	11
10	127	59	68	67	60	102	19	102	8	23	77	0	6
11	128	56	70	52	71	111	17	98	5	19	92	1	13
12	106	50	54	48	58	89	17	79	3	22	68	0	10
13	88	32	54	43	41	60	23	59	2	14	48	0	8
14	82	31	50	34	46	72	10	66	2	22	54	0	6
15	74	27	47	26	46	65	14	52	1	13	34	3	13
16	44	15	26	18	21	31	10	24	2	4	18	0	7
Total.....	1412	690	708	614	762	1164	253	947	50	231	849	19	180

With few exceptions these 1,412 children are twelve years old or less, so that they easily come within the ages that show the primary and secondary types of the disease. This group of children, chosen as they are because of known exposure and because of suggestive physical findings, represents a group in which a rather extensive tuberculization has taken place.

690 of these children were definitely exposed through association with open cases in the home.

614 gave positive skin tests.

Stereoscopic plates were taken in 1164 cases.
947 showed calcification of the hilum either upon one side or both.
849 showed the hilum moderately enlarged.
19 showed the hilum greatly enlarged.
231 demonstrated calcified primary foci.
180 plates showed a normal hilum.

This group of children, 1,412, gave histories of having suffered from ten major symptoms at the time of their first examination at Lymanhurst. Each child in the group averaged complaining of three symptoms each, as follows:

Coughs and colds	968	Nervousness	289
Run down	804	Chest pains	232
Enlarged superficial lymph nodes	566	Loss of appetite	196
Fatigue	536	Night sweats	174
Fever	461	Blood—spitting	21

Of this group there were 231, or sixteen per cent, who showed calcified primary foci in the lungs. Two hundred and twenty-two of these cases with primary foci showed calcified hilum nodes, and gave 23.4 per cent of all cases of calcified nodes. The symptoms of which the child complained when first examined were no more prevalent among these children than among those who showed no evidence of calcification of primary foci. Some symptoms complained of were even less frequent among children showing primary foci. Fever was one of the common symptoms complained of, and occurred among 461 of the children, or 32 per cent of all those examined, but only among 17 per cent of those who showed calcification of the primary foci.

While 43 per cent of the entire group of 1,412 children gave positive skin reactions, only 24 per cent of the cases showing evidence of primary foci gave the same reaction. Fatigue was present in 37 per cent of the 1,412 children, and in fifty per cent of those with calcified foci.

Forty-one children in this group were under two years of age, 25 of whom were under one year. Thirty-two were exposed to active cases of pulmonary tuberculosis. The skin reaction was positive in 18 of the 28 upon whom the test was reported. Stereoscopic plates were made of 31 of those children under two years of age; 5 showed calcification of the hilum, 2 showed primary foci calcified, 13 showed enlarged hilum shadows, and 28 normal hilum shadows. Tuberculization of these infants has not terminated quickly in the third stage of the disease; in fact, the invasion has occurred among members of this group very much

the same as in groups at higher age-levels. General disseminated tuberculosis has not occurred, and these children are doing as well as other children infected later in childhood.

From a study of these cases it would seem that the pathological classification applies to infants as well as to the later ages, and that infection frequently follows exposure during infancy without serious results.

The 1,412 cases here considered, many of whom have been exposed to positive-sputum cases of pulmonary tuberculosis, who show significant pulmonary changes clinically, and by skin reactions and by roentgenograms, constitute the potential sanatorium load of the future. Tuberculosis prophylaxis, as carried out at the Lymanhurst School, has demonstrated the effectiveness of such treatment in this group of children through the disappearance of symptoms, gain in weight, change in disposition and attitude towards play. This group of juvenile tuberculous (arrested) children, observed and treated early during the secondary stage of their disease, and reinforced by health habits, will be able, it is hoped, to carry their tuberculous bronchial lymph nodes through the vicissitudes of adult life without further reactivation of their juvenile infection or its extension into the lung parenchyma.

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BLOOD-CHEMISTRY CHANGES IN CHILDREN PRODUCED BY EXPOSURE TO THE ALPINE LAMP[1]

E. M. GREISHEIMER AND A. W. ARNOLD

It has long been held that tuberculosis is accompanied by a demineralization of the body, and calcium salts advocated in the treatment of this disease. Halverson (1) and his co-workers found that the normal amount of calcium in the blood was from 9 to 11 mgm. per 100 cc. The amounts in the blood of tuberculous patients varied from 8.4 to 11 mgm., thus showing no marked deviation from the normal. In the most advanced cases a slight reduction was found. This was in agreement with the results of some of the earlier investigators. Halverson found that the calcium values tended to be higher in blood drawn after the noonday meal than in the fasting condition.

Barkus (2) studied the blood calcium in 80 cases of surgical tuberculosis. His values ranged from 10.16 to 10.83 mgm., except in the atrophic type, when the average was 8.94 mgm.

An extensive study of the blood changes in tuberculosis was made by Sweany and his co-workers (3). They found no constant relation between the calcium content and the stage of the disease. In 6 hemorrhage cases the calcium was a trifle lower than in other tuberculous patients. The acid-soluble phosphorus was low in the advanced cases. The inorganic phosphorus was low in some favorable cases as well as in some severe cases.

McCluskey (4) studied the phosphorus distribution in the blood of tuberculous men. Her results indicated that in the more severe cases the lecithin phosphorus was decreased in both the cells and the plasma, while the acid-soluble phosphorus was increased.

Matz (5) found the normal calcium range to be between 9 and 12 mgm. The calcium of tuberculous patients was found to be within these limits. It would seem that low calcium values in tuberculosis are not the rule, except possibly in the far-advanced cases. The phosphorus metabolism does seem to be somewhat disturbed.

The effects of sunlight on the blood were called to the attention of medical men by Hess (6). He concluded from his results on rachitic

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children and experimental animals that sunlight could either cure or prevent rickets. He found an increase in the inorganic phosphorus of the blood, from 3.5 mgm. to 4 mgm. Surely this increase is so slight that we wonder whether it alone could be responsible for the "cure" of the condition.

Tisdall (7) studied the effects of ultraviolet rays on serum calcium and inorganic phosphorus in six rachitic infants. Before radiation the calcium varied from 7.7 to 9.1 mgm., and after radiation from 9.7 to 10.7 mgm. The increase was slight, but definite. The increase in organic phosphorus was more striking than in the result of Hess, being, in one case, from 2.8 to 6.7 mgm.

Kramer (8) and his co-workers found changes after ultraviolet radiation of rachitic infants comparable to those of Tisdall.

Interest in the effects of heliotherapy on the blood of tuberculous patients arose. Tisdall (9) found that heliotherapy did not increase the inorganic phosphorus content of blood serum in bone tuberculosis. Piccaluga (10) obtained results which disagreed with those of Tisdall.

Howe and Medlar (11) studied the blood changes in tuberculous adults undergoing Alpine-lamp treatment. They found that the calcium and phosphorus metabolism was normal in the tuberculous patients, and that the ultraviolet rays produced no effect upon the calcium or phosphorus content of the blood.

Clark (12) attacked the question of the effect of ultraviolet light on the condition of the calcium of the blood in a different manner. She used serum from dogs and rabbits. A part of the serum was radiated in quartz tubes, and then radiated and nonradiated samples were dialyzed. The percentage of dialyzable calcium was increased by radiation. The author suggests that the un-ionized calcium may be found electrically by the negatively charged proteins, and that radiation, by discharging the proteins, may free some of the bound calcium, thus increasing the percentage of ionized calcium.

Moritz (13) also studied the effects of ultraviolet radiation on the blood of normal rabbits. He found no changes in the total calcium, or in the diffusible calcium, either *in vitro* or *in vivo*, thus failing to confirm Clark's results. His method appears to be the more reliable.

It would seem from the above results that there is still considerable disagreement concerning the effect of heliotherapy on the blood of tuberculous patients, as well as on the blood of rabbits.

METHOD

These studies were carried out on children attending the Lymanhurst School for Tuberculous Children. Eight boys and 8 girls were selected.

The boys served as controls, receiving no Alpine-lamp treatment during the course of the investigations. The girls, after six weeks of observation, received Alpine-lamp treatments. The distance was thirty inches; the duration of exposure increased from one minute on the first day to twenty-five minutes within six weeks. The exposure was not increased beyond twenty-five minutes, although the observations continued for several weeks more.

The children, between ten and sixteen years of age, were cases of masked juvenile tuberculosis. They were afebrile during the four months of observation, and were able to attend school daily. Most of them were gaining in weight and strength, and several were ready for transfer to the public schools at the close of the observations. Since the children lived in their own homes (which were very humble ones), it was impossible to follow the diets, and this presents a serious objection to such studies.

At 11 A.M. the blood was drawn by syringe and transferred to 15-cc. centrifuge tubes containing between 1 to 3 mgm. of heparin. After centrifugation, the plasma was drawn off by pipette and the calcium determined by a modification of the Tisdall (14) method.

The total acid-soluble phosphorus of the plasma was determined by a modification of the Bell-Doisy (15) method. Improvements have been suggested by Briggs (16) and by Benedict and Theis (17).

The heparin was analyzed for calcium and acid-soluble phosphorus. No calcium could be found, although the determinations made on heparinized plasma were a trifle higher than those made on the serum of the control. The calcium in the serum was found to be 10.07 mgm. per 100 cc. In the heparinized plasma of the control, the calcium was found to be 10.64 mgm. Perhaps a bit of calcium remained in the clot, thus accounting for the slight difference in the two values. In the control, 4.2 mgm. of heparin were used per 10 cc. of blood, which was a more generous amount than was used on the children.

The amount of acid-soluble phosphorus in the heparin was extremely small. Since less than 3 mgm. of heparin was ordinarily used for about 12 cc. of blood, and only 0.25 cc. of plasma was used for a phosphorus determination, our values are only slightly higher than those for serum. In the control, the serum showed 12.48 mgm. of acid-soluble phosphorus per 100 cc. The plasma showed 13.3 mgm., a difference of 0.82 mgm. of acid-soluble phosphorus. It cannot be denied that this may be due to the heparin, since differences in acid-soluble phosphorus of untreated plasma and serum have not been determined.

We also realize that drawing blood between three and four hours after

breakfast is less desirable than drawing it before breakfast, but we had no choice in the matter in these cases. We realize that we are open to criticism on this point. We likewise realize that it would have been better to use some boys and some girls for controls, and others for treated cases, rather than to have had all boys for controls and all girls for the experimental group.

TABLE 1

Calcium content of blood serum

BOYS (CONTROLS)	NOVEMBER 23 AND 30	DECEMBER 7 AND 14	JANUARY 20	FEBRUARY 17	MARCH 3	MARCH 17
	mgm.	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*
C. T.	10.19	10.19	12.93	9.76	10.81	10.77
J. K.	9.94	8.09		10.40	9.66	10.71
S. S.		9.77	12.83	10.87	9.44	10.84
D. D.	9.86	10.02	10.23	11.63		10.66
R. G.	10.35	11.17	10.68	10.78	12.34	10.97
N. A.	9.86	10.35	11.40	10.60	11.93	10.64
L. W.	8.87	9.31	12.89	10.78	10.53	10.69
D. M.	9.53	10.35	10.84	10.02	10.97	10.06
Average	9.80	9.91	11.69	10.60	10.81	10.67
	First period, 9.85		Second period, 10.94			

TABLE 2

Calcium content of blood serum

GIRLS	BEFORE ALPINE-LAMP EXPOSURE			DURING ALPINE-LAMP EXPOSURE			
	November 23 and 30	December 7 and 14	January 4	February 10	February 24	March 10	March 24
	mgm.	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*
O. S.	9.53	9.86	9.64	10.44		11.06	10.63
P. T.	10.51	10.19	9.94	10.12	12.39	11.25	10.40
L. D.	9.11	9.31	8.62	10.12	12.39	10.08	10.43
E. R.	9.44	9.66	10.23	10.02		10.23	10.60
E. V.	9.94	10.60	9.66	10.19	11.60	11.28	10.64
I. S.	8.95	8.85	8.48		10.02	10.06	10.22
M. G.	9.61	10.74	10.05	11.13	11.33		10.40
H. K.	9.11	8.87	13.38	10.58	11.11	10.73	10.78
Average	9.52	9.76	10.00	10.37	11.47	10.67	10.51
	First period, 9.76			Second period, 10.75			

RESULTS

The corrected values for the calcium are given in tables 1 to 4. The results are expressed as milligrams per 100 cc. of heparinized plasma.

The time of observation was divided into two periods, the first extending from November 23 to January 4, and the second from January 5 to

March 24. It will be noticed in table 1 that the average calcium content for the first period was 9.85 mgm., and for the second period 10.94 mgm. Thus the boys, without any treatment, showed an increase of 1.09 mgm. of calcium per 100 cc. of plasma.

In table 2 it will be noticed that the girls showed an average calcium content of 9.76 mgm. during the first period, and during the second period an average of 10.75 mgm. The increase during the second period amounts to 0.99 mgm.

TABLE 3

Total acid-soluble phosphorus

BOYS	NO ALPINE-LAMP EXPOSURE					
	November 23 and 30	December 7 and 14	January 20	February 17	March 3	March 17
	mgm.	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*
1. C. T.	12.27	19.36	15.00	14.81	15.15	19.23
5. J. K.	14.18	14.70		16.26	15.03	16.12
7. S. S.	12.50	16.66	16.95	14.39	13.15	14.81
8. D. D.	12.04	14.08		13.07	13.42	15.74
9. R. G.	17.20	16.90	17.60	13.42	13.69	12.90
10. N. A.	16.40	16.90	16.00	12.50	13.30	14.29
13. L. W.	19.20	17.50	11.00	12.90	13.51	15.03
16. D. M.	14.80	12.90		12.19	14.29	12.57
Average	14.82	16.12	15.31	13.69	13.94	15.08
	First period, 15.47		Second period, 14.50			

TABLE 4

Total acid-soluble phosphorus

GIRLS	BEFORE ALPINE-LAMP EXPOSURE			AFTER ALPINE-LAMP EXPOSURE			
	November 23 and 30	December 7 and 14	January 4	February 10	February 24	March 10	March 24
	mgm.	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*
2. O. S.	13.24	16.12	12.57	12.50	13.79	12.04	16.00
3. P. T.	14.39	17.69	15.38	16.12	11.69	14.81	12.66
4. L. D.	11.90	14.20	11.90	13.30		11.83	12.82
6. E. R.	13.88	13.33	14.28	13.69	14.08	14.81	12.57
11. E. V.	16.00	12.70	10.64	13.07	14.59	12.90	12.50
12. I. S.	15.36	11.90	12.90	15.15	12.98	13.60	12.66
14. M. G.		13.70	11.76	12.04	12.57		13.60
15. H. K.	12.80	12.20		12.12	17.09	12.50	10.52
Average	13.94	13.98	12.78	13.50	13.83	13.21	12.92
	First period, 13.57			Second period, 13.36			

Consequently, we cannot say that Alpine-lamp treatment produced an increase in calcium content in these girls, since boys without any treatment showed an increase even slightly greater in extent.

The average acid-soluble phosphorus content in the plasma of the boys during the first period was found to be 15.47 mgm., as shown by table 3. During the second period it average 14.5 mgm., showing a decrease of 0.97 mgm.

Table 4 shows that the average acid-soluble phosphorus of the girls during the first period was 13.57 mgm. During the second period it fell to 13.36 mgm., a decrease of 0.21 mgm.

The acid-soluble phosphorus thus decreased in both groups, but the decrease is so small that it really is not significant. It would seem from these studies that Alpine-lamp treatment in such children has little, if any, effect on the acid-soluble phosphorus of the plasma.

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PRESIDENT'S ADDRESS[1]

THE PROBLEM OF NATURAL AND ACQUIRED RESISTANCE TO TUBERCULOSIS

THEOBALD SMITH

The President's address, coming as it does at the opening of the sessions, might well serve as a salutatory to welcome you to these meetings which should contain elements of education and recreation. This year the address comes between two intellectual feasts, one that is just closed, the other to begin to-day. The President's address can hardly escape being perfunctory under these auspices. It may be that in the distant past an address of this kind might have given tone and set the pace for the proceedings,—or shock by some unexpected utterances. To-day, however, the individual, whatever his title, plays only a very minor rôle on a stage set months and even years before. We live in the future, and the present is mortgaged to the past. I shall present, therefore, only a few stray thoughts which may take the place of the condiments in the intellectual foods to be set before you.

The National Tuberculosis Association is unique in the breadth and scope of its activities. Not only does it support researches on fundamental problems in the biological relation of the tubercle bacillus to the human host, but it enters the everyday life of the tuberculous patient and ministers to his immediate wants. Between these extremes are many activities tending to weld the organization into a homogeneous active unit and to bring the results of the best scientific thought to the amelioration and relief of suffering. It is not necessary for me to go into detail concerning the specific activities of the Association, for the monthly bulletins and the annual report of the Managing Director give you the main story of this smoothly working machine,—smooth because of the human factors giving their daily lives to it, and representing lay, expert and professional functions.

It is difficult to grasp the fact that forty years ago this highly organized machine or any like it did not exist. Those of us who are

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approaching, or have reached and passed the three-score-and-ten period of life, have watched, as adult professional workers, the beginnings and evolution of all these scientific and institutional agencies which are to-day active in the study and suppression of tuberculosis. To estimate the extent of the work and the lasting impression it has made on the general population, it is only necessary to recall the spitting habits of a generation ago. It was with great repugnance and disgust that one entered a public conveyance in those days.

Certain great evolutional trends are discernible during this span of forty odd years. The first was naturally a study of the newly discovered cause or parasite, the tubercle bacillus. Exploited from every possible direction, this microörganism has now been fairly well exposed in its movements from patient to patient. The great concern of the early workers was to suppress and destroy it, for with this accomplished there could be no more tuberculosis. It turned out, however, that the bacillus was so thoroughly embedded in the race and spread over the entire globe that at the present time the tubercle bacillus still exists. The conviction was thus impressed on the medical world that, while the number of tubercle bacilli in transit can be pushed close to the base line of extinction, a small residue will continue to function in view of the world-wide distribution of the disease and the world-encircling traffic. The ease with which this residue of bacilli may be reanimated and take renewed possession of the race was demonstrated by the world war.

The next great trend which dominates the work to-day was to turn attention from the bacillus to the patient, not because of any lessened consideration of the importance of the bacillus, but because it had been fairly harnessed and the machinery for its continued suppression had been well developed. At first the movement toward the patient was a mass movement, but it has come to be now one directed toward the individual. This evolution toward the care and treatment of the tuberculous individual at first manifested itself in the hospitalization of patients in the early stages, next in the segregation of advanced cases as a necessary corollary of preventive treatment. Lastly came the home treatment after the means for keeping vagrant tubercle bacilli in check had been satisfactorily conquered.

Following the bringing together of patients in institutions, public and private, and the application of environmental and dietary measures, the closer scrutiny of patients led to the development of surgical

methods of relieving the individual, all tending toward contracting and immobilizing the diseased lung tissue, and thus concentrating all forces on the tuberculous process, giving the parts that ample blood supply through dilatation of the entire capillary bed which is so effective in all reparative processes.

An important and significant recent venture of the National Association and local and State associations is to include in their program not only the specific fight against tuberculosis but the broader task of elevating the general health. The underlying assumption is that whatever raises and conserves the general health also contributes toward resistance to tuberculosis. Here again the general problem gradually splits into more specific ones, such as prenatal care, the health of the child, the prevention of injury to the heart, the guarding of the adolescent period, and the minor environmental factors of pure air, diet, physical culture, and the like.

The task of raising and conserving health presents a far more difficult and abstruse problem than the specific attack on tuberculosis. The latter is a delimited, positive one; the former an all-inclusive, negative one, in that it resolves itself not only into the many things to do but also the many to avoid. Like most phenomena of life, health may be represented by a curve, rising to a peak and falling. We should like to keep ourselves on the peak. The things to do represent the rising, the things to avoid the falling limb of the curve. From another standpoint we may look upon health as the maximum development of physiological functions but not their maximum use or exploitation. The best measures may be overdone. Hence there cannot be mass training in health except in a most general way. Each person is subject to a different health curve. What represents the upward slope for one may be the decline for another. When the farmer is taught to breed and feed his chickens to lay two eggs a day in place of one he is exploiting his flock in one direction. Sooner or later untoward factors will appear, due to deficiencies created by exhausting ovarian activity. Following a similar law the sum total of our energies has a more or less fixed maximum. If we overdevelop one function, we lose in another. No broadcast rules will therefore suffice. The individual cannot be entirely fused with the mass.

These facts are trite and well-worn, and I mention them only to emphasize the importance, first, of the individual as against the mass in health maintenance, and second the continued necessity for adjust-

ing health measures to changing conditions. We must not assume that we fully understand what health is, but continue to explore and research in all directions, since the normal must shift with changing conditions.

This brings me to the subject of research. Research is the development of new ideas from a base-line of fact and the testing of such ideas by some kind of work, either observation or experiment or both, to determine the soundness of the ideas advanced. Without a sound base-line of fact ideas simply represent the play of the imagination. Research is commonly regarded as some recondite occupation, open only to certain highly gifted individuals. It is true that some individuals and groups are apparently set aside to do research, but it is research of only a certain type,—research requiring numerous instruments for accurately measuring and weighing processes and results. But it is not limited to this kind if we accept the definition I have given. Not all research requires great accuracy. It is only when ideas developed by observation and experiment in the great field of nature and life are to be subjected to final tests that the so called scientific research begins. Among the members of this Association research is going on daily in the home, the sanatorium, the hospital, the dispensary and clinic, whenever new ideas or departures from current views are subjected by the originators to as many tests as they can apply with the means available, and particularly if they have ingenuity to manipulate their resources so as to devise new and more convincing tests of the soundness of the new ideas.

Moreover, when, as in tuberculosis, the same problem is attacked from several directions, each field of work has within its horizon data not accessible to other groups of workers. Only by coördination and coöperation can the subject be fully explored.

With the increasing density of population, the accumulation of knowledge, and the division of labor in producing it, the individual worker becomes of lesser significance, more one-sided, and perhaps more prejudiced in the direction of his special field of activity. The practical man, working on the surface among actual living conditions, fails to realize how vague and unsupported and often unsound his working basis and his postulates are. The highly trained laboratory worker, living among more or less precise instruments to aid his senses, on his part fails to realize that in many respects the more accurately controlled his experiments and observations and the more tied to instruments of precision, the further they are removed from practical use and the more

amendment and adjustment they will require to fit everyday existence. Only adequate coöperation and sympathetic understanding will make both extremes of service to humanity actually serviceable.

The Association, through a special committee, began some years ago to organize and develop coöperative research on what we regard as fundamental problems in tuberculosis. The tubercle bacillus is being followed into its lair,—the tubercle,—and the forces there opposed to each other segregated, if possible, and measured. That this is a desirable and even necessary, though not an easy task may be appreciated if we pass before us the host of questions that arise when such researches are planned. The behavior of the body in the presence of the tubercle bacillus once successfully analyzed and formulated would provide us with a guide which might very speedily decide the fate of any new remedies suggested, and eventually set our minds at rest as to the attainable in this disease.

All research is governed and regulated by hypotheses and theories which determine the direction the investigation is to take for the time being. We may formulate at least several theories concerning the relation between host and parasite in tuberculosis without meeting serious obstacles, but only one or perhaps none may be true. This means that we still lack important data of whose existence even we may not now be aware. There are two variable, adaptable organisms concerned: the animal body and the tubercle bacillus, each of which may act within an entire gamut of states thus yielding a large number of possible results. To this complex condition we must add the variable dosage of the tubercle bacillus which affects the outcome, thus adding to the possible variety of the final product,—the disease itself.

Having thus realized the complexity of the forces at work and the many conditions governing them, we find it necessary to utilize refined means of research to steady some of the forces while the others are at work. This can be done only by experiment in the laboratory. The unknown, unmeasurable variables must be balanced by adequate controls. We must carefully rear and select the animals and no less carefully the tubercle bacilli. We must keep the environment under control as to food, heat, light. The tubercle bacilli introduced into the animals must be approximately numbered. Thus the laboratory endeavors to control the details which cannot be regulated or measured in the clinic.

The research direct often receives its most potent suggestions from

collateral sources. Researches into the host-parasite relations of all other disease-producing organisms contain each and every one of them suggestions valuable to researches in tuberculosis if we only could clearly apprehend them. There is no host-parasite relationship which does not involve some one or more of the fundamental factors governing the tuberculosis process, for in the last analysis the general problem of parasitism stripped of its special, individual features underlies them all.

Even the somewhat alien researches in zoology led Metschnikoff to formulate the doctrine of phagocytosis as the essential element in the host-parasite contest. In theories and speculations concerning tuberculosis phagocytosis has played a prominent part. Metschnikoff traced this cell-function in the lowest forms as a mode of digestion into higher forms as a mode of protection from foreign invasion.

Let us now look somewhat more closely at our problem. Tuberculosis is named after the conspicuous, rather unique product of the disease, —the tubercle. What does it mean? The bacillus inhaled, ingested, rubbed into a fresh wound is carried from the place of original deposit to the nearest lymph node, probably within a leucocyte. Here its presence becomes marked by a certain type of mobile cell about it until the group becomes visible to the naked eye as a tubercle. After a time the cells of the tubercle degenerate, die, and are converted into a so called caseous mass forming the central portion of the tubercle. From mass the surviving bacilli may escape under certain conditions and form fresh tubercles in various organs and tissues. This is the story told us by the microscope in many variations. What happens to this picture in the highly immune and the highly susceptible races and species? How is it modified in these extremes? It is obvious that the tubercle does not sterilize itself, for the caseous material is infective. Even calcified tissues may contain living bacilli.

The question then arises whether the tubercle is the whole story or whether it is only a fragment. What is the significance of the cellular gathering? Is it the decisive factor, or are there humoral factors governing it from a distance, and do other cell groups contribute humoral agents to control the tubercle? Are the processes which we can define reactions indicative of susceptibility, are they reactions indicating resistance, or has every one an element of both in it? Is the tide turned one way or another by forces inherent in the tubercle or generated outside?

We know that soluble substances escape from the tubercle; otherwise it would be impossible to account for the hypersensitiveness, both local and general, of tuberculous subjects to tuberculin. In the same way other products of the tubercle bacillus may pass out, be disseminated, and start immune reactions in the body where appropriate cell-groups are found.

Processes, at first protective to the host, may be modified through natural selection, so as to become compromises or even of advantage to the parasite. Thus phagocytosis, originally a process of nutrition of the cell by intracellular digestion, has in some instances become modified so as to afford shelter for the parasite and even opportunity to multiply. So in most highly specialized infectious diseases, the phagocytic process has been made inoperative because the parasite possesses new specific functions not subject to intracellular digestion.

Perhaps the most extreme example of the dominance of the parasite in tissue reactions is furnished by the galls on the leaves and stems of plants. Due to the prick of insects each gall is more or less characteristic of the insect causing the injury and developed only on certain species of plants. The gall is not a protective reaction of the plant but a home for certain stages of the special insect. The host is entirely passive. The tissue reaction may have perhaps started as a protective gesture, but manoeuvered, through evolutionary processes covering long periods of time, to the exclusive advantage of the insect.

It is worth while to recall the well-known fact that the tubercle is not such a highly specific structure as we might hastily assume. Monocytes are characteristic of the tissue-reaction to paratyphoid and typhoid bacilli. The tubercle is partly reproduced when neutral foreign bodies lodge in tissues and in the presence of animal parasites. The gathering of one type of cell is not in itself indicative of any formidable defense reaction. It is rather specific for the irritant set free. Thus, certain bacteria attract polymorphonuclear leucocytes, while animal parasites bring together immense numbers of eosinophiles. It is quantitative, and only to a certain degree qualitative, conditions to be measured in the study of the focal reaction to tubercle bacilli.

If we pass in review the situations I have briefly sketched we might answer them hypothetically in several, even mutually contradictory, ways. This means that still further analysis is necessary before we may safely formulate a working hypothesis which will account for resistance

as well as susceptibility. This hypothesis will have to put a qualitative as well as a quantitative value on the factors I have mentioned, or those into which these factors may be resolved by research.

Some of the factors mentioned will be dealt with in the coming sessions of the Association, and my review of the problems is designed merely to put you in a receptive state of mind, and perhaps stimulate you to continue to think on these problems and endeavor to fit them into your own work, and perhaps turn the scales thereby toward more productive research within the laboratory and without.

Although a study of what goes on in the tubercle may be regarded as fundamental, it is after all only the focus where all the forces governing tuberculosis come to a head. Hence, without a broad knowledge of all factors, even though ill-defined, the student of the host-parasite relation is poorly prepared for his task. One of these dominant studies is what may be called the epidemiology of the disease, all those conditions and antecedents which govern the incidence of tuberculosis in any group or even in the entire world population. Among the striking facts developed by statistical data is the steadily falling death-rate from tuberculosis. This is accounted for, on the one hand, by the sanitary achievements of the past half century; on the other, by profound biological forces more or less independent of public health advances. Like so many data subject to controversial debate the decline is probably due to both agencies. Given a more or less static relation to an environment which changes but slightly, all epidemics die out sooner or later, or else slide down to an endemic level of low mortality. An adjustment between host and parasite seems to take place very gradually in some diseases, more rapidly or even abruptly in others. In tuberculosis the downward trend of mortality must have been greatly hampered by the world-wide intercourse, growing in intensity, which has distributed universally all types of tubercle bacilli, some probably much more virulent than others. Even under this adverse condition, under which a population growing in density has been compelled to digest, as it were, all types of tubercle bacilli, a decline in mortality has taken place; and here the growth of sanitation and preventive medicine, coupled with an environment growing in general anti-infectious forces as a result of a higher level of material resources, must have played a dominant rôle.

Unfortunately, mass statistics leave much to be desired, owing to necessarily primitive classifications. Mortality is a poor basis for

estimating the significance to the race of any slowly progressive disease like tuberculosis. Yet it is perhaps the best attainable. It is to be hoped that each investigator coming in touch with large numbers of tuberculosis patients will develop statistics of his own, based not merely on death-rate, but on morbidity, on the main localization of the infectious process, on the intensity of the process, and perhaps on other significant characters. There still remain the family relations, the environment, the age-period, and last, but not least, the main characters of the infecting agent. Gathering such data is in the order of research and part of a final synthesis of the whole problem.

Intimately associated with the epidemiology of disease is the normal or natural resistance of the race or species. All animals, including man, possess a certain degree of resistance to infectious diseases independent of any preceding infection. This differs toward different infectious agents, and individuals differ from one another in their resistance to the same disease. So variable is this individual resistance that in the employment of animals by the investigator he resorts to the use of large numbers and to statistics to average his results.

This natural resistance has been contrasted with what is called acquired resistance due to the use of vaccines and serums, and previous attacks. Acquired resistance is only a specific increment of natural resistance, either through temporary mobilization of natural forces or the more prolonged overactivity of some element of natural resistance. Thus, in horses treated with diphtheria toxin for a period of several years, the antitoxic content of the blood may still be high one year after cessation of treatment. So the guinea pig, treated with a toxin-antitoxin mixture when young, is capable of transmitting later on through the placenta the product of an active immunity to successive litters of young over a period of two to three years or as long as such animals can be kept alive. But the animal body does not control all diseases as easily as it does diphtheria toxin. In tuberculosis the natural resistance of civilized races is relatively high, but it seems difficult to produce a specific augmentation of this resistance. If this is true, it follows that any temporary reduction or exhaustion of such natural forces is not easily made up and should be avoided.

Hitherto acquired resistance has been the object of intensive study because of its association with the appearance in the blood of the so called antibodies—agglutinins, precipitins, antitoxins, bacteriolysins, bacteriotropins, and others. These bodies are of great interest in

furnishing focal points in the study of specific immunity and in incidentally furnishing valuable material for all kinds of diagnostic tests. It is fortunate that attention is now being gradually directed toward the natural fund of resistance and the constitution of individuals studied with reference to this fund. Draper refers to four panels of personality, or hereditary unit characters, found in anatomy, physiology, psychology and immunity. It is this fourth group of unit characters which governs the natural or inherited resistance to disease.

The results of studies in the congested urban centres of Europe and this country have shown that a large proportion of children have been infected with tubercle bacilli. In the absence of a pronounced natural resistance active tuberculosis would have been the expected outcome, since experimentally the young are the most susceptible. This latent infection is stirred up later by active, voluntary or involuntary, infringements of health-laws, which probably lower temporarily the fund of natural resistance.

Speculations, anticipations, hypotheses have been rather frowned upon in scientific circles as affecting adversely the stimulus toward actual demonstration. But there are two sides to the matter. Some hypotheses can never be adequately demonstrated or disproved by actual experiment and they must receive their fate more or less indirectly. In the meantime they may serve as valuable aids in suggesting directions. In this spirit I suggest the following hypothesis.

The primary resistance of the host is due to forces inherent in the system. According to the amount present on the one hand and the infecting dose and the virulence on the other, these resisting forces are wholly or partially used up and only gradually replaced. When they are below a certain level, the disease process takes a jump and will go on unless overtaken by the level of normal resistance. During this process, certain antigenic factors of the tubercle bacillus tend to stimulate and raise certain specific elements of the natural, resisting system. These in excess would disturb and perhaps check the tubercle bacillus. They are, however, developed very slowly. On the other hand the level of the natural forces is restored by what we may call healthy living, whatever that may prove to be.

This hypothesis does not negative or discourage possible discoveries toward specific aids in the struggle against tuberculosis. In fact, it implies two definite possibilities: first, discovery in the healthy, resisting individual of those normal, natural factors which tend to

suppress the tuberculous process; and, second, isolation of the specific factors raised from the natural level by the disease process. These elements may not lead to a miraculous cure, nor will any yet to be discovered. The discovery of insulin, a remarkable achievement in adding to the system a deficient factor, does not cure diabetes, yet no one will hesitate to acknowledge its great positive value to the race.

If the foundation of all immunity resides in natural, inherited or genetic tendencies, it is reasonable to assume, until researches in this field shall have led to more definite results, that this immunity may be lowered and partly lost temporarily by all conditions which tend to lower general health. From this standpont it is highly fortunate that this Association and associated organizations have broadened the antituberculosis movement into a general health campaign. Anticipating further discoveries in the domain of natural immunity, we are justified in emphasizing the importance of a maximum development of normal functions, in the hope that some or all contribute to this natural fund of resistance to tuberculosis.

Nothing in biology is foreign or alien to the problem of tuberculosis, for parasitism is a universal phenomenon of life and tuberculosis is merely a special manifestation of this phenomenon. We wish to rise above it as we do above all parasitism which we have largely inherited from our geological ancestors. This desire is one of the marks which distinguish us from our brute ancestors. The cost is high. It represents a very material fragment of what we call hygiene and public-health administration. Infection is an unwelcome guest in any pathological state, and it leaves behind a trail of undesirable conditions. As the late Dr. Hermann M. Biggs has categorically stated in another way, *Health is purchasable.* But we cannot have the purchase money for this as well as for many other activities. We must choose and make sacrifices. We cannot raise ourselves to a level of health and stay there without continual effort. We are in fact perpetually mortgaged to health.

A DISCUSSION OF CERTAIN FUNDAMENTAL PRINCIPLES INVOLVED IN HELIOTHERAPY

F. M. POTTENGER

Heliotherapy is an attempt to apply the radiant energy of the sun to the treatment of disease. As in all therapeutic procedures, technique and dosage are extremely important. In order to use the sun's rays intelligently, one should know those factors which increase or decrease the amount of solar energy available for therapeutic purposes. It is equally important to know the effect of the energy upon the physiological reaction of the patient. Anything that will give information along these lines will help to place heliotherapy upon a sane and sound basis. In this paper it is my desire to discuss some of these problems.

SOURCES AND FINAL DISTRIBUTION OF SOLAR RADIATIONS

The sun, directly and indirectly, is the source of most of the energy existent in our world. It has been estimated that the centre of the sun sustains a temperature of 9,000°F. The sun is influenced by gravitational forces the same as the earth. Its atmosphere also is subject to many changes. Some of the important phenomena which have been carefully studied in their relationships to the radiant energy of the sun are sun-spots, the solar constant, electrical and magnetic disturbances, and various currents and storms which seem to correspond to winds and cyclones in the terrestrial atmosphere. These phenomena produce variations in the amount of radiation emitted from the sun and cause changes in the earth's atmosphere, which, in turn, influence the passage of radiant energy to the earth's surface.

The energy emitted by the sun follows certain cycles. At times, when increased energy is put forth, volumes of gas are projected into space for great distances,—thousands of miles. Scientists consider that of all the disturbances in the sun's atmosphere, the study of sun-spots is most helpful because longer and more accurate records have been kept of these than of other phenomena. The solar constant, which is a measure of that portion of solar energy which reaches the earth and is converted into heat, is also a subject of importance for study, but available records extend over only a few years, too few for basing conclusions.

There has been much speculation as to the cause of sun-spots and also as to the regularity of their cycles. It may seem strange to those of us who have learned to think of the sun as the centre of, and the greatest force in the universe, the master of everything, to know that there is much evidence to show that its disturbances in energy are due to influences exerted upon it by other heavenly bodies, particularly the planets.

The period from one time of sun-spot maxima and minima to the next represents a cycle of about eleven or twelve years, with other cycles, not so exact, of shorter and longer duration. It is suggestive that Jupiter requires about this same major period of time (11.87 years) for making a revolution around the sun; and, further, that the sun-spot maxima are related to the time that Jupiter is at perhelion. Other planets exhibit a smaller influence as follows: taking the earth as 1, Jupiter is 35.5, Saturn 3.2, and Mercury 2.5. An appreciable maximum effect on the sun's mass is exerted by each planet when in conjunction with Jupiter, and a minimum effect when in opposition. Then there are numerous combinations of influences of all, as may be imagined. The effect of these planets on the sun's mass is similar to that of the moon on the earth in producing ocean tides; but, in the case of the sun, the disturbance manifests itself in the form of huge masses of energy being projected out into space instead of as oceanic tides.

Inasmuch as our changes of climate and weather depend very much upon changes in solar energy, and inasmuch as changes in solar energy depend upon forces exerted upon the sun by the various planets, we can see how the entire solar system is linked together in the production of atmospheric disturbances of the earth. The most important terrestrial atmospheric disturbances are changes in temperature, pressure, electrical and magnetic force, and wind and storms.

The effect of sun-spots upon climate and weather, and the effects of the sun's radiant and electrical energy upon the human being are just now beginning to be appreciated. While there are many terrestrial factors to be taken into account, variability in the sun's energy is the most important cause of our daily and weekly weather changes.

Since sun-spots are due to the ejection out into space of large bodies of gas, heated to high temperatures, one would think that times of maximum sun-spots would be times of high temperature on the surface of the earth. Such would be the case were it not for the fact that, when gas is ejected out into space in great volumes, tremendous terrestrial disturbances follow. Cyclonic storms of great severity occur in various parts of the

earth, and the air movements connected with them protect the earth's atmosphere from the effects of the increased heat.

The proper conception then is that the sun is a varying source of radiant energy, one from which now more and now less energy is emitted, the amount changing from day to day and also over longer periods of time. Among conditions which affect radiant energy are latitude; altitude; the condition of both the upper and lower atmosphere; the content of the earth's atmosphere in water-vapor, dust and smoke; wind movement; storminess; and the altitude of the sun in the sky.

Solar radiations consist of waves of many different lengths, each differing from the other in the degree with which it is transmitted to the earth and in its action on things upon the earth. Rays between 4.000 and 8,000 Ångstrom units make up the visible spectrum. The long waves are heat-rays, and the short ones are chemical rays. The shortest visible ray is 4,000 units, and there are many beyond which are shorter, some approaching zero units in length; so are there many longer than 8,000 units. Most of those which are shorter than the shortest visible rays are screened out by the ozone in the upper atmosphere and do not reach the earth. Helland, Hansen and Nansen estimate that 40 per cent of the sun's total emitted energy is lost by reflection, 40 per cent is absorbed in the upper air, and 20 per cent reaches the earth. This 20 per cent is made up mostly of waves longer than the ultraviolet, for the shortest wave reaching the earth from the sun is 2,900 units.

The radiant energy absorbed in the upper atmosphere exerts an important effect upon the temperature, electrical reactions, atmospheric pressure, wind movement and storminess of the earth.

The following measurement of radiation, just below the shortest visible rays taken at the Mt. Wilson Laboratory at an altitude of about 6,000 feet, illustrates the difference in the transmission of rays according to the position of the sun in the heavens. The relative number of radiations of different lengths when the sun is at its zenith and at 75° altitude shows how the short rays are screened out in passing through greater depths of atmosphere, as they do when the sun is low in the heavens.

		Length of rays in Ångstrom units					
		3,000	3,200	3,400	3,600	3,800	4,000
Relative amount of rays when	Sun at zenith	25	58	135	192	239	302
	and						
	Sun at 75°	2	8	26	49	74	117

While the short rays are screened out by the ozone of the upper atmosphere, they readily pass through water and hence are not influenced so much by the water-vapor of the air. They are absorbed, however, by the smoke and dust of the atmosphere. The long rays, on the other hand, are not influenced so much by the ozone of the upper atmosphere, but are absorbed by the water, smoke and dust found in the lower atmosphere. Therefore, the amount of radiant energy which reaches the earth varies greatly in different places, and increases or decreases the desirability of the place for residence as well as from the standpoint of health and comfort.

SOLAR RADIATIONS AND PLANT LIFE

One of the most interesting experiments showing the value of light to the animate world was performed by the late Benjamin Moore in conjunction with Webster. They exposed carbon dioxide in water, in the presence of uranic and ferric hydroxides, to sunlight, and produced formaldehyde. Formaldehyde being a forerunner of sugar, this work proved experimentally that the organic can be made from the inorganic.

This experiment affords a peep into the laboratory of the plant, as it is played upon by sunlight, and explains the production of carbohydrates. In the presence of the chlorophyl and its pigments which are found in the cells of plants, light acts upon carbon dioxide in the presence of water, and produces starches and sugars. This light-energy is converted into chemical energy, and is stored in the plant to become the great source of food for animal life.

Sugars are built up by the action of sunlight, and fats are elaborated from sugars, but protein must be produced from nitrogen. Moore showed that nitrates in dilute solution will absorb light-energy and be changed to nitrites, and that the cells of green plants can absorb these nitrites and build up nitrogenous substances. Nitrites are deposited upon the leaves of plants as rain and dew, whence they are absorbed under the stimulation of light.

Sunlight is necessary to the plant's metabolism. Neither sugar, fats nor proteins can be synthesized by the cells without it. With light and the chlorophyl acting as catalyst, the bulk of the energy of the animate world is produced and stored in the plant kingdom; but even without chlorophyl a certain degree of synthesis will go on with the production of oxygen. The chlorophyl itself is synthesized by sunlight acting upon iron salts found in the chloroplast of the plant.

Chlorophyl contains magnesium, without which it would be powerless to store or transform energy, the same as hemoglobin would be without iron. Both are powerless without sunlight. Whereas through the action of sunlight upon colloidal iron in the chloroplast, chlorophyl is built up from inorganic compounds, and through the action of sunlight upon chlorophyl, starches, sugars, fats and proteins are synthesized with the setting free of oxygen, hemoglobin acted upon by sunlight causes the breaking down of the food which the plant has synthesized, and thus liberates the energy necessary to animate life and action, with a setting free of carbon dioxide.

SOLAR RADIATION AND ANIMAL LIFE

In a discussion of the action of light upon the body there are certain basic facts which claim first consideration. Man must be considered as a mass of cells, orderly arranged and depending upon impulses received from various sources for their activity. These cells represent different and changing colloidal systems, which respond to stimulation by taking up or giving off important ions during the course of their activity. There are two sources of radiant energy in the world: first, the sun, and, second, the radiant energy that is given off from radioactive substances. Stimuli, however, are of many kinds, such as sound, light, heat, odor, taste and touch, each of which is received and transmitted to the body through sensory receptors. Food has been created by the sun's energy and stored in plants, after which it has been eaten by animals and again stored in their bodies. In this manner all food which is consumed by man goes back to sunlight. The ability of the body-cells to utilize the food also depends upon the sun's energy.

Before one can understand the action of radiant energy upon the body, he must grasp the fundamental principle that body-cells are receptors and transformers of energy. There can be no action without absorption of energy; furthermore, there can be no action unless the absorbed energy is transformed into energy that is suited to the activity of the particular tissue. Radiant energy probably acts in two ways: first, upon the sensory nervous system which thickly studs the surface of the body; and, second, upon the blood and tissues themselves, which absorb radiant energy and transform it into substances suited to the requirements of the cells themselves.

Not only does man have receptors throughout the body which pick up

stimuli, and cells which act as transformers, but he also is obliged to unify and correlate or integrate all action. The integrative systems, which mould the bodily organism into a whole, are the nervous and the chemical. These two systems distribute energy in such a manner as to keep the whole physiological organism working harmoniously.

There seems to be a close relationship between the sun's energy and calcium metabolism. Just what this is, we are unable to state definitely. We know that in summer months, when the sun's energy is greatest, the blood-calcium is increased. The meaning of this, however, is not clear. It may not be due alone to the greater activity of the sun's rays, but may only accompany it. It may be due to the necessity of the retarding influence of calcium upon cellular activity during the warmer season, when the demands upon the metabolic activity are not so great. This, however, will require further observation to determine.

We know clinically that the sun's rays will aid in the prevention and cure of rickets. It is thought that the influencing of calcium metabolism is an important factor in the result obtained. We also know that sunlight will aid pregnant women in maintaining a normal level of calcium metabolism. The effect of sunlight on the tuberculosis patient is also associated with a rise in blood calcium.

Experience shows that either solar radiation or radiation by ultraviolet rays from artificial lamps will have the desired therapeutic effect. This is particularly interesting because we are prone to consider the ultraviolet as the essential rays in the therapy of these maladies. Experiment shows that very few ultraviolet rays reach the earth, yet solar radiation is effective. It must be that we are too narrow in our view, and that our bodies are able to obtain from light, whether it be the radiant energy of the sun or the radiant energy of ultraviolet lamps, those substances which are essential to maintaining a normal calcium metabolism, or to the restoration of it when disturbed.

PHYSIOLOGICAL AND THERAPEUTIC ACTION OF RADIANT ENERGY

Body-cells react differently to radiations of different wave-lengths. The reaction also differs according to the amount or dosage of radiation, no matter what the quality of the ray. It is essential in discussing sun-treatment not to assume that it is either good or bad, beneficial or harmful, but to assume that each individual may have sun-treatment according to his own powers of utilizing light and still maintaining or improving his physiological balance.

Sunlight, direct and indirect, differs greatly in its content of radiant energy under different conditions, some of which have been enumerated herein. Even reflection from the clouds and from the sky carries with it large quantities of solar energy, which produce very important effects upon the physiological mechanisms of the body, and which can also be utilized in the treatment of the sick. Light which passes through ordinary glass loses by absorption much of its shorter rays. So light in houses, passing through closed windows, is deficient in its power to promote well-balanced physiological activity. No doubt, that light which is unobstructed by glass windows is responsible for some of the good effects produced by an open-air life. There has been too much of a tendency to think of solar energy as a force which, in some mysterious way, produces a direct antibacterial effect, and which destroys germs and cures infections; but such is not the case. In the world at large, sunlight is our great destroyer of bacteria, and even in the animal body, if we count the effects of its indirect action, we must give it first place. But, according to our knowledge, we cannot claim much for radiant solar energy as a direct disinfectant of body-tissues, for the penetrating power of the short rays which reach the earth and which are known to possess strongest antibacterial effects, is very slight. Finsen showed that ultraviolet light penetrates the skin only a fraction of a millimetre, and in order to treat lupus successfully he found it necessary to press the blood out of the tissues by some material which was transparent to the rays. This does not mean, however, that ordinary sunlight cannot aid man in making his body a vigorous physical machine or in restoring it, if weakened, to a state of vigor so that his natural defensive forces will be able to overcome infections. It has been shown that the infrared rays have bactericidal qualities, and it seems quite probable that the body-cells may utilize light of all wave-lengths in its indirect antibacterial action.

Aside from the effect of radiant energy acting through the sensory nerve fibres found upon the body-surface, it alters the oxygen tension of hemoglobin which absorbs it, and in this manner influences the activity of body-cells. It has been shown that oxyhemoglobin parts with its oxygen more readily in the light than in the dark; the heat rays most likely take a very important part in this action. The temperature of the part exposed to direct sunlight may be raised several degrees; and it is well known that both chemical and biological reactions are hastened by moderate increases in temperature. Hemoglobin, aside from the rays of the visible spectrum, readily absorbs infrared and ultraviolet radiations,

the latter from between 4,000 and 2,900 from the sun and down to 1,850 from the quartz light.

The radiant energy from the sun is the most natural and probably the most important of all stimulants to the physiological activity of the body. It is the duty of physicists in conjunction with physiologists to determine the action upon the organism of various forms of radiant energy found in light. We assume that all wave-lengths, from the longest down to the shortest chemical rays, are of value, but that their action differs according to the particular properties of the waves. It is certain, however, that man has adapted himself to the light to which he is accustomed, so that he is able to maintain perfect physiological equilibrium no matter where he lives. This holds for the tropics, the temperate zones, and the polar regions; for the lowlands, the plains and the mountains; for areas of desert dryness, as well as for areas of rain and abundant moisture. Man is also able to change from one condition to another, and adapt himself to the radiant energy content of the atmosphere of the new habitation.

All solar radiations to which the physiological mechanism has adapted itself are useful in maintaining normal health, and valuable in restoring it when injured by disease. This fact is not sufficiently taken into consideration in the discussion of heliotherapy. I believe we are focusing our attention too much upon ultraviolet radiation to the detriment of the patient. Physicists tell us that few ultraviolet rays reach the earth in the regions most thickly populated, yet no one can doubt the beneficial influence upon the health of people which results from exposure of the bare body to sunlight.

If we accept the symptom complex shown by a patient in the presence of a given disease as *the manner in which his physiological mechanism is able to function in spite of the disease*, we then will be able to apply therapeutic measures such as heliotherapy more understandingly. We will see that they are valuable to the extent that they will aid the body to carry on its functions in a manner as near to normal as possible.

Heliotherapy must not be confused with the therapeutic employment of ultraviolet light. Sunlight, direct or indirect, can be utilized advantageously in the treatment of many diseases. Patients, who for any reason should not be exposed to the direct rays of the sun, frequently can be advantageously exposed to the indirect rays as found in diffuse light. Diffuse light does not contain as many rays as direct sunlight, but it does

contain rays which are of value to the body in carrying out its many functions.

Indirect sunlight can be applied advantageously to those patients suffering from active tuberculosis who are not suited to treatment by direct solar radiation. Bare arms, bare chest, or very thin clothing are valuable in that they expose the patient to larger doses of radiant energy.

Ultraviolet rays have a special action. While they are not found in large quantities in the earth's atmosphere, yet they have been shown to be very desirable for certain effects which are often sought. Fortunately, they can be generated artificially by certain lamps and used therapeutically. They are taking a permanent place in the therapy of tuberculosis and also in the treatment of other conditions.

In the investigation of this subject the following works will be found helpful:

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HELIOTHERAPY IN PULMONARY TUBERCULOSIS[1,2]

WILLIAM C. POLLOCK[3]

Heliotherapy is now universally employed in extrapulmonary tuberculosis and results obtained have been extremely satisfactory. The method is being more and more extensively used, and its wider application has resulted in closer attention to details and better technique. It has also stimulated study of the various problems encountered, and this intensive study of heliotherapy throughout the country will result in still more gratifying results in treatment.

Since about 30 per cent of all cases of extrapulmonary tuberculosis are complicated by pulmonary tuberculosis, heliotherapy has been very frequently applied to cases with pulmonary disease. It has been noted that in such cases the pulmonary lesions clear up remarkably well. One might explain this rapid improvement by stating that such patients are treated under ideal conditions and that rather rapid improvement is to be expected. They are bed-patients, are out of doors day and night, have nourishing food, are in good general condition and, as pointed out by many clinicians, they have the added factor of increased resistance through the possession of an extrapulmonary lesion. Extrapulmonary foci do not heal as rapidly under all the above conditions if heliotherapy is not used. Pulmonary cases, treated under ideal conditions, in general do not show improvement at the rate observed in extrapulmonary cases complicated by pulmonary tuberculosis under heliotherapy routine.

This brings up the question, "Why not treat pulmonary tuberculosis by sunlight?" At present the question is a much discussed one.

Rollier writes, "It has often been said, and is still believed by many, that heliotherapy is dangerous and its application powerless to help in cases of pulmonary tuberculosis. We hold a different opinion and our experiences tend to prove our contention. It is true that most of the cases that we have treated accompanied surgical lesions." He is convinced, however, that helio-

[1] From the Fitzsimons General Hospital, Denver, Colorado.

[2] Published by permission of the Surgeon-General, U. S. Army, who is not responsible for any opinion expressed or conclusions reached herein.

[3] Captain, Medical Corps, U. S. Army.

therapy, properly applied, would be a useful agent in the treatment of a great majority of cases of pulmonary tuberculosis. He thinks that results have been sufficiently good to encourage his colleagues, whose experience in this disease is greater than his, to make a serious attempt to apply systematized sun-treatment to *suitable* cases. However, Rollier continues to confine most of his attention to nonpulmonary manifestations of the disease.

T. and J. Stephani observed a large number of cases that showed retrogression under heliotherapy, which they attributed to overdosage. They state that the chest must not be insolated in pulmonary tuberculosis for more than a few minutes each day. Armand-Delille advises against heliotherapy in pulmonary tuberculosis. Bacmeister, using rather long periods of exposure, reports unfavorable results. On the other hand, Malgat used rather short exposures and reported favorable results. Renon and Szaboky obtained satisfactory results in selected afebrile cases. Haberling and Von Schrötter both admit satisfactory results, but explain that these were obtained by factors other than by direct sunlight.

Hervé and Roussel are convinced that much good may be derived from sun-cure carefully carried out, and that most of the ill effects, which from time to time have been reported, have been due to errors of technique or unwise selection of cases. They have had eleven years' experience with heliotherapy and are rather enthusiastic regarding their results. Webb and Gardiner speak of fair results in the treatment of pulmonary cases, while Shortle believes heliotherapy should be used.

McCutcheon regards heliotherapy as most valuable in pulmonary tuberculosis. He reported 105 cases, and found the most marked effect to be a decrease of moisture in the lung. He noted improvement in sleep and appetite and gain in weight, with no change in temperature and pulse.

Bronfin states that heliotherapy does not yield encouraging results in far-advanced cases, but he does not attribute favorable or unfavorable effects entirely to heliotherapy. He considers it as dangerous as tuberculin if injudiciously used, and notes resemblances in the bodily reaction, caused by heliotherapy and by tuberculin. He reports a series of 50 cases, but 31 had extrapulmonary involvement.

LoGrasso and Balderrey report a rather detailed study of 49 cases. Seventy-seven per cent were improved and the greatest value of heliotherapy was manifested in an improvement of the patients' general condition. Clinical symptoms indicated diminished activity of the

pulmonary process, and the blood picture and mental attitude of the patients were improved.

Watson advocates heliotherapy for extrapulmonary tuberculosis alone or when complicated by pulmonary tuberculosis; and states that it is of some value in some cases of the productive type of pulmonary tuberculosis, but practically never of value in the exudative form. He advocates extreme caution in its use if there is any pulmonary involvement. He is of the opinion that the air-bath may prove to have most or all of the advantages of heliotherapy with none of its disadvantages.

Many others have used heliotherapy in pulmonry tuberculosis with both favorable and unfavorable results. In Switzerland, where this method of treatment was first used, it has been practically discarded for pulmonary disease.

From a review of the literature, which is more or less confusing and does not assist greatly in estimating the value of heliotherapy in pulmonary tuberculosis, provided the opinion of each clinician is given equal weight, one may draw either of the following conclusions:

1: Heliotherapy is an unsatisfactory method of treatment in pulmonary tuberculosis.

2: Heliotherapy is a satisfactory method of treatment, and unsatisfactory clinical results have been due to injudicious dosage or unwise selection of cases for insolation, or to both.

Any one who has observed heliotherapy judiciously employed in properly selected cases cannot entertain the first conclusion. Taking the literature in its entirety one finds considerable variation in the period of insolation employed, but the more recent literature indicates rather close adherence to the schedule advised by Rollier. Since there is more or less uniformity in the period of exposure, the chief difficulty would seem to exist in the selection of cases. Let us consider some opinions as to the types of cases suitable or unsuitable for treatment with sunlight.

Rollier states, "The sun should be dispensed, so to speak, drop by drop when nearing the region of the thorax. Needless to say, no patient with high temperature, nor one who is passing through a period of acute evolutionary intoxication should be exposed to the sun."

Hervé and Roussel say, "The types of pulmonary disease for which it is especially indicated include mainly cases of pleural and glandular involvement,

fibrous types and tuberculous laryngitis. Of particular value associated with artificial pneumothorax and its complications, especially pyothorax." T. and J. Stephani remark that "only torpid stationary forms are suitable for this treatment." Fecht, using the quartz lamp says, "Stationary cirrhotic forms are suitable. The exudative type, especially with cavities, may become worse." Pottenger exposes febrile cases. McCutchen classified his series of 105 cases as follows: incipient 5, moderately advanced 45, and far advanced 55. Of his cases 60 had moderate toxemia. Bronfin classified his series of 50 as follows: far advanced, active, bilateral, 40; far advanced, inactive, fibroid, 8; moderately advanced, active, one; moderately advanced, inactive, fibroid, one. Lo Grasso and Balderrey in their series of 49 cases give the following classification: first stage, 7; second stage, 37; third stage, 5. Watson does not give his figures, but reports experience with both productive and exudative pulmonary tuberculosis.

From the above review it would seem that the greatest diversity of opinion in treating pulmonary tuberculosis with heliotherapy lies in the selection of cases. Taking into consideration the marked diversity of results and that the chief difference among workers has been the selection of cases, it seems that the problem which demands intensive study is the type of case suitable for heliotherapy.

At the direction and under the supervision of Lt. Col. Earl H. Bruns we have made an attempt to determine the value of heliotherapy in the various manifestations of pulmonary tuberculosis.

Our cases were studied in three different groups. Group 1 consisted of 30 advanced pulmonary cases; group 2, of 10 more or less border-line, active-inactive cases; and group 3, of 72 fibrous convalescent cases.

Group 1: The advanced pulmonary cases were selected from a ward of 100 patients. They had not responded favorably to the ordinary hygienic treatment. However, they presented only mild toxemia with only slight afternoon elevation of temperature. Practically all had rather extensive cavitation and several were complicated by tuberculous enteritis. In no instance was the chest exposed to the sun. The Rollier schedule was followed, and treatment was supervised daily by the physician in charge. It was soon found that many cases of this group were unsuitable for heliotherapy, and the treatment had to be discontinued to 15 of them on account of an increase of toxemia. Treatment of the other 15 cases was carried to the completion of the study. Of these cases 4 showed improvement, 3 were stationary and 8 were progressive. Exposures were given only with early morning sun, and the duration of exposure

was decided by the individual's reaction, the maximum exposure being one hour.

Group 2 consists of 10 cases selected for detailed study in an effort to determine just what type of pulmonary involvement was suitable for sun treatment. Of this group 4 cases were classified as fibrous; 2, borderline fibrous, caseofibrous; and 4, caseofibrous with definite activity and cavitation.

In this group the cases were carefully examined and X-rayed, and all routine laboratory examinations were repeated prior to the administration of treatments. These examinations were repeated at frequent intervals, a chest X-ray being made monthly.

The method of solar exposure as applied to this group was a modification of the Rollier schedule. The body was divided into zones, according to Rollier's method, and exposure made of zone I, consisting of feet and ankles, on the first day; and zone II on the second day, while doubling the exposure for zone I. Instead of exposing for a period of five minutes, as is usually done, only two-minute exposures were used, and the chest was not exposed until the remainder of the body showed maximum pigmentation.

When the maximum degree of pigmentation had been attained and prior to exposing the chest, the following observations as to progress of the cases were made: The 4 fibrous cases showed improvement by clinical signs and X-ray, the general condition was improved, and there was a gain in weight and a decrease in cough and expectoration. Blood counts showed a reduction in total leucocytes, with a relative increase of lymphocytes, red cells, and hemoglobin. The two border-line fibrous, caseofibrous cases were stationary as to lungs and general condition, but their cough and expectoration decreased. Their blood picture improved. The 4 caseofibrous cases showed progression of pulmonary involvement: 2 gained weight, one was stationary and one lost weight, but cough and expectoration were decreased in all. Their blood picture remained practically unchanged. Our study of these cases was then continued by exposing the chest with extreme caution and using very small zones of exposure and two minutes as the unit of exposure. The maximum exposure depended entirely upon the individual patient's reaction. There was considerable variation of the period of insolation tolerated by the cases. The maximum exposure of the chest attempted in any case was two hours.

Patients presenting fibrous lesions of the lungs could tolerate an

exposure of two hours to the chest, while one of the cases with caseofibrous pulmonary lesions was unable to tolerate any exposure of the chest. Exposure of this group continued for from four to six months.

Let us now repeat our observations as to progress. The results in fibrous cases were practically the same; they all showed improvement according to accepted standards. The border-line fibrous, caseofibrous cases remained stationary. The caseofibrous cases retrogressed. As unfavorable symptoms appeared, an attempt was made to ascertain the proper period of exposure suitable to such cases by gradually reducing the exposure of the chest. We did not succeed in this, for when too much perifocal reaction is produced the patient will not react favorably to the sun-bath unless the period be reduced considerably below that which he is capable of withstanding after the reaction has subsided.

Group 3, our next study, consisted of fibrous cases. These were what we term convalescent cases. They had been under our care for a considerable time, taking routine hygienic treatment. They had progressed favorably, and the pulmonary foci had become largely fibrous. This is the type of case suitable for graduated exercise.

This group consisted of 72 cases, and in this type the Rollier schedule was followed, and the maximum exposure of two hours attained without unfavorable reactions by practically all cases. As in the other groups, the cases were treated individually, modifying the schedule when necessity required. They responded very favorably; their general condition improved, they gained weight, a rapid completion of fibrosis with focal contraction ensued, their appetite was improved, and their vigor was increased. It is rare to find a fibrous type of lesion not responding favorably to the sun-bath. In this group only about 25 per cent received insolation of the chest.

In all of our studies the patients followed a strict routine of hygienic treatment in addition to heliotherapy. They remained out of doors day and night and, when weather permitted, took air-baths of long duration, often spending the entire day with nothing on except a pair of trunks.

Advanced cases of pulmonary tuberculosis, with caseofibrous, fibrocaseous or caseous lesions, are unsuitable for heliotherapy. Such cases usually have symptoms of toxemia, their general condition is below par, they show an elevation of temperature easily, and many already have perifocal reactions about the pulmonary lesion. In such cases insolation of the extremities for a short period will often produce an unfavorable pulmonary reaction. Pulmonary lesions react to the sun-bath much

more sensitively than do tuberculous foci elsewhere in the body. Advanced cases of pulmonary disease complicated by tuberculous enteritis show considerable symptomatic relief when the abdomen is exposed to the sun's rays daily. This area is relatively small, and can usually be exposed from thirty minutes to one hour without unfavorable pulmonary reaction.

We depend partially upon a favorable perifocal reaction around the tuberculous lesions to bring about fibrosis and healing. In most cases of advanced active pulmonary tuberculosis perifocal reaction is already present to a degree which is in excess of a favorable reaction. Should this reaction be increased by exposure to the sun, the end-result can be none other than progression of the process. The same reasoning applies to cavities, for most cavities in advanced cases have walls more or less thickened on account of inflammatory reaction to the tubercle bacilli and because of numerous other microörganisms in secondarily infected cavities. An increase of this reaction will result in enlargement of the cavity.

In advanced cases which, through surgical procedures, such as artificial pneumothorax, phrenectomy or thoracoplasty in its various forms, have reached convalescence and no longer show toxemia, heliotherapy should be employed. We use it routinely with marvelous results in all cases of the surgical service that have undergone extrapleural thoracoplasty.

Active cases respond favorably to heliotherapy when the activity is not sufficient to produce toxemia. The greatest caution possible must be exercised in administering sun-rays to them. One must proceed, so to speak, inch by inch and minute by minute, and the chest should not be exposed.

In toxic cases unable to take sun-baths, air-baths under shelter should be instigated until healing, with lessened toxemia, makes sun-baths feasible.

Inactive fibrous lesions respond favorably, and improvement continues even after exposure of the chest. One may think that after reaching this stage they should do well and an uneventful convalescence be expected; however, these selected cases were of patients whose condition had been stationary for some time, and improvement or healing sufficient to warrant return to duty seemed unlikely at an early date.

It is in the convalescent cases of pulmonary tuberculosis in which the foci are essentially fibrous, that the best results are obtained. During treatment of this stage of the disease the patient is only too often

neglected, inasmuch as the attending physician is no longer so solicitous of the patient's condition, and the doctor's attitude often gives the patient a false sense of security. He is prone to go beyond the prescribed limit in his activities. Heliotherapy in this type of case serves a two-fold function. In addition to furnishing the patient with definite routine, which impresses him with the fact that he still requires treatment and the attention of a physician, it affords him a method of treatment unsurpassed in its power of building up his tissue resistance and ensuring him a type of lesion favorable to prevent further infection from within.

The response of pulmonary tuberculosis to heliotherapy is not comparable to the favorable response in extrapulmonary tuberculosis. Let us consider six factors in explanation of why pulmonary tuberculosis does not react well to heliotherapy:

First: Pathological study of pulmonary and extrapulmonary lesions shows a difference in chronicity. The pulmonary lesions, although chronic in nature, present an acuteness not observed in ordinary extrapulmonary lesions. The more chronic, that is, the more productive the lesion is, the more likely will there be a response to treatment. The productive nature of the process indicates tissue resistance.

Second: Pulmonary lesions are so often more widespread. In the lungs are histological and physiological factors which favor the spread of the disease. The soft, vascular, ever-moving tissue of the lung promotes the dissemination of foci by continuity, by the lymph and by the blood. The bronchial tree makes possible the spread of infection by aspiration from diseased to healthy portions of the lung. These factors may soon convert a favorable into an unfavorable lesion under even the strictest regimen of treatment.

Third: Pulmonary lesions vary much in age. While one portion of the lung may present fibrous lesions, another portion may have caseofibrous foci, and with these it is possible to have an aspiration focus, caseous and at the base. In such instances heliotherapy, while of advantage to the fibrous lesion, would be disastrous for the caseous lesions elsewhere.

Fourth: Pulmonary lesions are deep-seated as compared with the general run of extrapulmonary lesions, and are therefore beyond the power of penetration of our most effective therapeutic rays. Observations in cases of extrapulmonary tuberculosis have taught us that the more superficial the lesions, the more satisfactory are our immediate results of treatment. This is especially to be noted in sinus formations; superficial sinuses close readily, while deep sinuses close only after

several years and often not then. Tuberculosis of the ankle and elbow responds quickly and the knee moderately well, but the deep-seated hip joint very slowly. A sinus-tract from a tuberculous ankle closes; one from the lumbar or dorsal spine is the most discouraging lesion with which the heliotherapist has to deal.

Fifth: Secondary infection is a factor of outstanding significance when the lesion is deep-seated. This factor undoubtedly plays an important part in the pulmonary lesions which are always secondarily infected. Secondary infection in extrapulmonary tuberculosis prolongs treatment fourfold, and is often the deciding factor between life and death. In secondary infections response to treatment depends upon the extent and depth of the sinus. The sinuses from secondarily infected cervical lymph nodes close; the sinuses from the secondarily infected tuberculous spine do not.

Sixth: Immobilization, one of our important adjuncts in the treatment of extrapulmonary cases, cannot always be carried out in pulmonary cases. When immobilization of the lung can be achieved through induced pneumothorax or extrapleural thoracoplasty then many of our factors which make heliotherapy inadvisable are eradicated, and we then have a case which will respond favorably to heliotherapy.

Cold-abscess formation is Nature's way of expelling broken-down tuberculous tissue from tuberculous lesions. Cold abscesses do not always form because often the broken-down tissue is not so extensive but that it can be absorbed in and around the foci.

In active confluent lesions heliotherapy, as it has been applied at the Fitzsimmons General Hospital, favors the formation of cold abscesses, inasmuch as it causes a rather rapid breaking down of the severely involved tissue, certainly more rapid than that observed in unexposed cases. This cold-abscess formation may be considered a preliminary step in the process of healing.

In lymph-node, bone and joint tuberculosis cold-abscess formation can easily be taken care of by aspiration, which prevents sinus formation and secondary infection, especially if a superficial joint is involved. In deeper joints one must often delay aspiration until the abscess approaches the surface.

In the lungs the same process of liquefaction takes place, cold abscesses form and burrow into a branch of the bronchial tree, the contents are coughed up, as purulent sputum, and the result is the formation of cavity. Such cavities always become secondarily infected from the

respiratory tract. As a rule, cavity formation is to be considered a serious complication, for cavities of the lung heal very slowly, if at all, and increase the danger of hemoptysis, bronchogenic extension and visceral degeneration.

The most favorable result of the sun-bath is an improvement in general condition accompanied by a stimulation of all bodily functions. Appetite is improved, digestion aided, and elimination increased by the activation of cutaneous function; sweat-glands function to such an extent that the individual loses from one to two pounds through perspiration during two hours of sun-treatment in midsummer. With this amount of fluid eliminated through the skin the kidneys are still kept well flushed; and the urine does not become concentrated because of the increased intake of fluid during the sun-bath, since patients have a desire and are encouraged to drink freely during their exposure and throughout the day. The musculature is improved; those muscles, which have become atrophied through inactivity during the more acute stage of the disease, regain their normal size and tone, even though the patients remain relatively inactive.

Weight is put on rapidly, and individuals who have been underweight since the onset of their disease regain or even surpass their normal weight. This gain in weight is not due entirely to an increase of fat; but more to a regeneration and hypertrophy of muscle fibres. Seldom do cases tend to become obese.

With general improvement there can be nothing but an improvement of the pulmonary foci. We thus have two factors to cause pulmonary healing; one, the indirect action of the sun, causing improvement of the general condition; and the other, a direct influence, which induces a favorable reaction around the tuberculous lesions.

In discussing the results of sun-treatment one should not overlook the psychological reaction of the patient, to whom any improvement or cure of disease effected by a natural method is always awe-inspiring. Laymen want no stronger evidence of the potency of a medicine than a guarantee that it has been brewed from natural herbs.

In the case of heliotherapy we find the patients regarding the treatment with awe. Their medicine comes from a heavenly body, created by the creator of life. They exhibit a psychological point of view not understandable to the physician who has not practised heliotherapy. No form of treatment in tuberculosis is received more enthusiastically by them. Their mental attitude is improved, their morale is high, and

their routine ward-treatment is carried out with a spirit unknown in the average tuberculosis ward.

Moreover, the sun-bath during both morning and afternoon with an air-bath at midday, together with other necessary ward routine, keeps the patient occupied throughout the day. He is moved in and out, receives this and that attention, hears enthusiastic remarks about his progress, and soon becomes a sunlight addict.

In the large majority of cases favorable results are obtained by general insolation without exposing the chest; and, when results are entirely satisfactory without it, we are of the opinion that it is well to continue insolation, certainly for a long period, without thoracic exposure. The chest should certainly not be exposed until the remainder of the skin surface has reached its maximum pigmentation. In lesions with any activity perifocal reaction can be readily produced without sunning the chest. The period of the sun-bath must be kept well within the bounds sufficient to produce reactions causing abnormal temperatures. If the perifocal reaction is enough to set up fever we have then gone beyond the limit of a favorable reaction. A perifocal reaction marked enough to be interpreted as such in the X-ray film is also in excess of a favorable response. We must rely upon the composite estimate of temperature, pulse, physical and X-ray examination and subjective symptoms of the patient, as a guide in heliotherapy.

Since we repeatedly warn against exposing the chest to the sun's rays in cases of active pulmonary disease, the question of the penetration of the rays is obviously significant.

The degree of penetration of light has been much discussed. The literature on the subject is very confusing, chiefly because of marked differences in the method of conducting experiments. Different types of light, ranging from the sun to the small incandescent light, different types of photographic plates to register the penetrating light rays and different methods of filtering out rays have been employed; and many authors are not explicit as to the rays capable of penetration.

Practically all agree that the ultraviolet rays have only slight penetrating power and probably do not go beyond the layers of the skin. Finsen states that the short ultraviolets are absorbed by the epidermis, and the long ultraviolets reach the capillary network of the deeper layers of the skin. Jansen and Bach found that the ultraviolet rays penetrated from 0.5 to 0.8 mm. Russ penetrated sections of skin from the abdomen with them. Rollier and Mierowsky advanced the theory that

the short ultraviolets are changed to longer and more penetrating rays upon entrance to the pigment of the skin.

Finsen stated that the penetrating power of the different colors is inversely proportionate to their capacity to produce inflammation. Malgat, Finsen, Kime, and others have proved that sunlight will penetrate the human body. They obtained impressions of objects upon photographic plates by passing sunlight through the human chest. Gebhard demonstrated that the light from an electric arc could penetrate the palm of the hand. Busck, using red, orange and yellow rays, was able to photograph through the hand in five seconds. Kaiser, by filtering out all except the blue and violet rays, obtained an impression upon a photographic plate through the chest. Lenkei, with blue and yellow rays, penetrated tissue through a distance of one inch, and this distance was increased to three inches when muscle was absent. Schamberg took a photograph through the cheek. Schmidt found that it required one second for the passage of red rays through fatty tissue, and one minute for their passage through muscle of the same thickness. Balderrey and Ewald obtained penetration to a depth of ten inches of human tissue.

The fact that ultraviolet rays do not penetrate beyond the layers of the skin does not mean that they are entirely absorbed by the skin, for many rays are disposed of by reflection and diffusion. Since the ultraviolets have so little power of penetration, one may wonder how results are obtained in treating deep lesions. Shall we assume that the action upon deep lesions is indirect, or that the long-wave rays which do penetrate deeply have beneficial effects yet unknown to us?

Wiesener found that infrared rays, especially those approaching the red, were bactericidal. They have great penetration on account of their long wave-length, and can thus exert an action on deep-seated lesions.

Much of the study on penetration has been done by filtering out all rays except those to be studied. It is believed that figures thus obtained cannot be used as representing the depth of penetration in administering heliotherapy, because of the probability that the action and penetration of the various rays are different when they are used in association with other rays.

In the case of sunlight, in which rays ranging from infrared to ultraviolet are used, it is believed that certain rays show increased bactericidal properties and increased penetration because of an associated action. Experiments along this line are difficult of performance by the physicist,

as the photographic plate is usually used to record penetration, and therefore rays cannot be associated, or any conclusion drawn regarding individual penetration.

Artificial methods, employing various screens to produce in concentration the rays thought to be beneficial, have not met with the clinical success obtained with sunlight. The best results have been had with that artificial light which most nearly approximates sunlight. This circumstance would suggest that the effective rays are intensified through their joint action with other rays, which, when used alone, have no beneficial qualities, and only exhibit these when used in association with rays of known qualities.

Another frequently discussed factor concerning the results of heliotherapy is pigmentation of the skin, which is the natural response to the irritation by ultraviolet rays. Pigmentation acts as a screen, for protection against further irritation and possible injury from the ultraviolet rays, and it regulates the action of the heat-rays of the solar spectrum.

Pigmentation, however, is considered not only a protective agent against insolation, but it also favors penetration by changing short nonpenetrating rays into longer and more penetrating rays. It transforms a white, reflecting skin-surface into a dark, light-absorbing surface, which really allows an increase in the intensity of sunlight endured, and therefore becomes of value to the patient who has reached the stage of greatly increased tolerance to radiation. Periods of radiation can be prolonged in well-pigmented individuals because the dark skin-surface acts as a heat radiator at an increased rate. Pigment likewise possesses biological value, from its being able to increase the activity of the elements essential to metabolism.

Block has demonstrated that a substance, very similar to adrenalin, when submitted to the action of an enzyme of the epidermis, produces the formation of a normal epidermic pigment, light strongly accentuating this formation. Jesionek suggests that pigment is split by light and taken up in the blood, to exert a therapeutic action. Rollier has noted a fairly close parallelism between pigmentation and a favorable prognosis. Hyde and LoGrasso state that the favorable prognosis of the case is in direct proportion to the intensity of the pigmentation of the skin, and they use the degree of pigmentation as an index in prognosis. Bronfin also states that pigmented cases show the most improvement, while Breiger can observe no relation between pigmentation and prognosis. Rost believes in allowing periods of depigmentation to intervene, so

as again to be able to produce essential erythema. Reyn and Ernst attempted to avoid pigmentation.

Heliotherapists, in general, make every effort to avoid erythema, which is likely to occur during the early period of treatment, and at this time extreme care should be used to avoid an unfavorable reaction. The toxic result of a generalized erythema is apt to produce an unfavorable reaction.

The rate and degree of pigmentation of the skin in the normal individual exposed to the sun are in direct ratio to the individual's natural pigment; that is, one can take a normal individual and estimate fairly well the amount of pigmentation which will result from exposure to sunlight. The normal true brunette will pigment deeply and the normal true blonde will pigment but little. If we take these two same individuals and suppose that each develops a tuberculous spine of practically the same degree of involvement and that each is treated by heliotherapy, how can the comparative degree of pigmentation be used as an index of prognosis? If the rate and degree of pigmentation can, in these two cases, be so used, then we may as well admit that the brunette possesses more tissue resistance to tuberculosis than does the blonde.

Pigmentation can be used as a guide in prognosis in the case of individuals who possess the same degree of natural pigment and who present practically the same degree of tuberculous involvement. In these we shall find that the patient who pigments more rapidly and more deeply is the one with the better prognosis, all other things being equal.

One can take a given case and estimate the degree of pigmentation that should develop, and if the degree of pigmentation falls far short of the original estimation the prognosis is not so favorable.

The decided brunette, with natural pigment indicating that he should pigment deeply under heliotherapy, but with massive tuberculous involvement, general anaemia, marked loss of weight, and poor general condition, will show slow and poor pigmentation.

The patient who pigments rapidly and well can be subjected to longer periods of irradiation without skin symptoms of insolation. The decided blonde has to be exposed in a more cautious manner or else skin erythema results; and, in addition to the discomfort to the patient, our routine of treatment has to be terminated, or continued with a diminution of the period of exposure.

The question of duration of exposure is not one of how much exposure the skin will endure, but rather of how much reaction one wishes to

produce around the tuberculous foci. While an individual may pigment rapidly and well and can stand rather vigorous exposure as far as his skin is concerned, it might be that the tuberculous foci, present in some other part of his body, are highly active and unable to withstand insolation to any degree. On the other hand, the unpigmented individual whose skin will not tolerate routine exposure may have tuberculous foci which are fibrous, without perifocal reaction, and capable of withstanding rather vigorous heliotherapy.

When one is preparing the schedule of treatment of a new case, the tuberculous foci should be the index to determine the amount of heliotherapy to which the patient should be subjected, and not the reaction of the skin to the sunlight.

A patient should finish his sun-bath with a feeling of stimulation which should last for the next few hours. A feeling of fatigue, depression, headache, decrease of appetite or elevation of temperature indicates that the sun-bath has been prolonged beyond the individual's tolerance.

Factors of no little significance in heliotherapy are meteorological conditions, composition of the atmosphere, and temperature of the air. A different technique must be used at the sea-shore than high in the mountains.

Of equal importance with location is the state of the atmosphere, especially as concerns foreign constituents, such as dust particles, and fog, clouds and water vapor. Water vapor forms an appreciable percentage of the total atmosphere, a percentage that depends chiefly upon temperature in the sense that, for any given pressure, the higher the temperature, the greater the possible percentage of water vapor. Because of this relation to temperature its volume per cent decreases in a lower atmosphere from the equator toward the poles. Humidity is mentioned in detail because of the marked variability in the intensity of ultraviolet rays due to factors such as humidity, smoke, dust particles, etc. Best results are therefore obtained where these factors are at a minimum. The beneficial results of heliotherapy are chiefly due to the ultraviolet rays, which are activated and accelerated by luminous and heat-rays; therefore, since ultraviolet rays are easily diffused, an atmosphere which undergoes less diffusion of light, because of diminished molecular diffusion caused by less water vapor and dust particles, is the most suitable for ultraviolet-ray treatment with sunlight. We find such an atmosphere at higher altitudes.

The importance of such factors can better be determined when we

consider the total loss of radiant energy. The rate of solar output of energy, distance from the sun, length of day, and solar altitude are all of vital importance in determining the amount of radiant energy delivered per unit of horizontal area during any interval of time. But they determine only the quantity of insolation delivered, and not the amount of energy actually absorbed and thereby rendered effective in maintaining temperature. Much of the energy is reflected and scattered. All solar radiation which is reflected back into space, whether by clouds or by the surface of the earth, is immediately and completely lost, and the same thing is true of that smaller portion lost through the process of scattering, whether by dust particles or by atmospheric molecules. The total loss of insolation by these two processes amounts to about 37 per cent for the whole earth. In other words, more than one-third of all energy delivered to the earth is unused, and merely scattered to space.

Temperature is important as a factor in the administration of heliotherapy, whether it is hot or cold, whether there are marked daily or seasonal variations, etc.

The variations of temperature of the atmosphere, both as to time and place, and also the actual average temperature for any given locality, are all obviously of greatest importance within themselves, and of equal importance indirectly through such meteorological elements as humidity, precipitation, direction and velocity of the wind, and nearly everything else that constitutes the sum total of both weather and climate.

At higher altitudes we have less water vapor in the atmosphere, fewer foreign particles, less cloud, a decreased rainfall in summer, and dry snowy winters. There is also less seasonal variation in the ultraviolet-ray content of the sunlight.

Climate therefore influences the sunlight to such an extent that there are bound to be marked differences in the results of heliotherapy. These may be so marked that one heliotherapist may report improvement of types of pulmonary tuberculosis by exposing the chest, and another may report such types as unsuitable for heliotherapy.

Heliotherapists, treating the same types of cases with the same schedule of treatment in Switzerland, Nice, France, New York, Pennsylvania, Kansas, Colorado, Arizona and California, and reporting results for comparative study, would be like observers using a certain drug and failing to take into consideration enormous differences in dosage. What may be a therapeutic dose of sunlight in one locality may be a toxic dose in another.

We would again emphasize the fact that heliotherapy must be applied to the individual according to his needs and not as a routine procedure to a group of cases. It should be used without interruption. In any locality there are certain seasons when sunshine is greatly diminished, and during such a season the patients should receive artificial-light therapy. Continuous therapy prevents the unfavorable reactions often experienced in cases in which the heliotherapy schedule is interrupted. We prefer the carbon-arc light for the reason that it is the light whose rays more nearly approach those of the sun and therefore gives the best results. The carbon-arc lights can also be purchased in the solarium type and a large number of patients treated at the same time.

Heliotherapy has been developed until it has become our most important adjunct in the treatment of fibrous pulmonary tuberculosis, and with its conservative use we produce a more rapid convalescence, and can discharge the patient with the assurance that he possesses a more complete and permanent healing of his tuberculous foci.

CONCLUSIONS

1. Heliotherapy is of the greatest value in the treatment of pulmonary tuberculosis during the convalescent stage when foci are essentially fibrous.

2. It is of value in the more active cases when exposure is regulated to the individual's requirements.

3. The chest should not be subjected to insolation in active pulmonary tuberculosis under any circumstances.

4. The remainder of the skin surface should be well pigmented before insolation of the thorax is attempted.

5. In advanced pulmonary tuberculosis the chest should be screened when treating extrapulmonary lesions.

6. Pulmonary lesions are more sensitive to sun-rays than are lesions elsewhere.

7. Cavities with perifocal reaction are enlarged by exposure to sun-rays.

8. Toxemia, resulting from pulmonary activity, precludes the use of the sun-bath, but air-baths should be given to such patients.

9. The greatest value of heliotherapy lies in the improvement of the patient's general condition.

10. Systematized exposure, such as that used by Rollier, or a modification of it, should be adopted in administering sunlight.

11. Heliotherapy requires the supervision of a physician and should be administered according to the patients' needs.

12. Insolation produces favorable blood changes.

13. Early morning sun should be used in summer and the maximum exposure should be two hours. In winter, midday sun can be used, and the length of the exposures increased. This conclusion applies only to the sun in Colorado.

14. Periods and times of exposure may be varied according to meteorological conditions, composition of the atmosphere and temperature.

15. Sun-baths have a favorable effect on the patient's mental attitude.

16. The perifocal reaction produced by exposure to the sun is similar to that produced by tuberculin.

17. Artificial light must be substituted for sunlight when sunlight is not available.

18. Convalescents from thoracoplasty improve rapidly under heliotherapy.

19. Penetrability and therapeutic action of rays depend upon associated factors.

20. Pigmentation is a natural protective reaction to the sun's rays, and is a valuable prognostic index.

THE EFFECT OF SANOCRYSIN ON THE TUBERCLE BACILLUS AFTER LONG EXPOSURE IN VITRO[1]

H. C. SWEANY AND MAX EVANOFF

In a former publication Sweany and Wasick (1) reported the direct effect of sanocrysin on the growth and viability of the tubercle bacillus. However, they observed certain phenomena in that work that they were unable to interpret. Among other things, it was noticed that the exposure of tubercle bacilli to various concentrations of sanocrysin for three months still left microörganisms that were sufficiently virulent to kill guinea pigs and produce peculiar abscess-like formations in the parenchymatous organs. It was observed also that, in many of the tubes containing tubercle bacilli to which sanocrysin was added, there were growths of non-acid fast bacilli that were at the time thought to be contaminations. Their appearance with such regularity in "pure cultures" caused us to investigate the problem. This report deals with microörganisms that were recovered from guinea pigs dying after injections with tubercle bacilli that had been exposed from one to three months to sanocrysin.

In the previous study a group of guinea pigs was inoculated intracardially with these treated bacilli, and these animals were killed after 18 days. All presented some form of disease that resembled tuberculosis, but many typical qualities were lacking. For example, the hilum lymph nodes were enlarged, the spleen was enlarged an average of twofold, the liver was mottled with small punctate abscess-like formations, and the lungs had a few scattered transparent granulations resembling early miliary tubercles. In these granulations partially acid-fast granulated bacilli were found when the cut-sections were stained.

The whole process was repeated in another series of animals. Guinea pig A17 received about 20 mgm. of tubercle bacilli exposed to 1–2,000 sanocrysin and died in 66 days; A18 about 20 mgm. of 1–5,000 and died

[1] From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

in 67 days; A19, 1–20,000 and died in 64 days; A20, 1–100,000 and died in 70 days; A21, 1–200,000 and died in 70 days; and A22, 1–1,000,000 and died in 61 days. All control animals lived. The type of pathological changes was much the same in every instance. There was marked hepatitis with an occasional abscess-like formation, the spleen was dark red and enlarged two to threefold, the lungs were markedly hyperemic, and there was in most animals a deposit of fibrin over the surface of the liver. The gall-bladder was distended with turbid bile, and the duodenum was markedly inflamed around the ampulla of Vater and for about 1 cm. below. The lymph follicles of the intestines were enlarged, and the contents of the intestines were fluid and bubbling with gas. The lymph nodes of the mesentery were sometimes much enlarged, as were also the nodes at the hilum of the lung. The outstanding fact was that the involvement in these animals resembled a septicemia more than a tuberculosis. In every organ, in the blood-stream, and in the abscesses there were always found great numbers of motile, gram-negative, bipolar, diplo-bacilli, quite variable in morphological, cultural and staining characteristics, but sufficiently like the colon-typhoid-dysentery group to be placed there tentatively.

These microörganisms were recovered in pure culture, and inoculated into guinea pigs. At the same time macerated pieces of spleen were inoculated into guinea pigs. The results were compared to see whether these microörganisms were responsible for the pathological changes, or whether some other virus that we were unable to grow was acting. Only a few protocols will be described because of the similarity of the various reactions. The microörganism no. 34 from guinea pig A18 was obtained in pure form by colony purification, and 1 cc. of the dextrose-bouillon culture was injected intraperitoneally into guinea pig L65, 0.01 cc. into L62, and 0.0001 cc. into L73. L65 died in 48 hours, L62 was killed in 3 months, and L73 died in 3 months and two days.

The protocols are as follows:

L65: Local site is swollen and hemorrhagie; inguinal lymph nodes markedly enlarged; the peritoneum contains 2 to 3 cc. of seropurulent fluid. The liver is pale grayish-yellow, with fibrinous deposits over part of the surface. The gall-bladder is distended with turbid bile. The lungs are slightly congested and have a pinkish-red color. The spleen is slightly enlarged with dark red pulp. The intestines are inflamed, especially the duodenum below the ampulla of Vater; the heart is normal; fatty changes are present in the kidneys

and adrenals; the mesenteric lymph nodes are enlarged, but not the hilum lymph nodes of the lungs.

L62: Was similar to L65, except that there were a large number of yellowish abscesses over the surface of the liver, measuring 1 to 2 mm. in diameter. The spleen was enlarged fifty per cent. The hilum lymph nodes were enlarged. Other organs were the same as those of L65.

L73: Was practically the same as L62. There was nothing particular about the microscopic examination that was unusual. Of L65 the liver has a marked amount of fatty changes; the spleen is markedly hyperemic with hyalinization of connective-tissue trabeculae, but there are no tubercles nor abscesses; the lungs are hyperemic, with markedly thickened alveolar walls; the duodenum has a thickened wall and a mucosa that is eroded in many places; the kidneys have fat in the convoluted tubules.

Simultaneously, some macerated spleen from A18 was injected into L21 and L26, both of which died of symptoms similar to the others, and cultures were made from the spleens and compared.

Likewise, some macerated spleen of guinea pig A19 was inoculated into L19 on August 21, 1925, and the animal died on September 1, 1925. Because of the unusual pathological changes, a detailed description will be given, as well as that of L82 inoculated in series from L19 by macerating a small bit of spleen removed aseptically.

L19: Local site is inflamed; inguinal lymph nodes are slightly enlarged; retroperitoneal glands are enlarged; and there are fibrinopurulent deposits over the surface of the liver and intestines. There are numerous adhesions between the loops of the intestines. The liver is a mottled yellow and reddish-brown. There is a large suppurating lymph node in the loop of the duodenum. The spleen is enlarged three times, is dark red, and is spotted with small white to grayish abscess-like formations, measuring about 1 mm. in diameter. The lungs are hyperemic, and the hilum lymph nodes are enlarged, the kidneys are yellowish, and the adrenals are fatty and slightly enlarged.

Microscopic findings: The lungs are hyperemic, and have a few clusters of pus cells resembling an early abscess or tubercle; the liver is fatty with an occasional group of partially necrotic cells; the spleen has a large number of miliary abscesses, with pinkish necrotic centres and a cellular border of polymorphonuclears and epithelioid cells. The cells at the border are elongated and arranged radially; there are a few such abscesses in the adrenal; there is nothing unusual in the other organs.

Bacteriology: Direct smear reveals a motile gram-negative diplo-bacillus of quite different morphological characteristics in different organs. It is usually bipolar (somewhat resembling the glanders bacillus), gram-negative and motile.

Cultural: On liquid media there was a rather marked turbidity, a slight

ring, and no sediment or pellicle. On solid media (plain agar) there was a slightly raised grayish-white filiform growth. The growth spreads in 48 hours, with clear isolated colonies at the upper end of the streak; potato has a slight shiny growth; gelatin has a nail-head growth but no liquefaction; indol and acetyl-methyl-carbinol are not formed; nitrates are reduced; nitrites are consumed and ammonia is formed. Milk is rendered slightly acid but is not coagulated, but there is no proteolysis in ten days. Acid is formed in dextrose, lactose, galactose, levulose, dulcite and mannite. Gas is formed in levulose, dextrose, mannite, galactose and dulcite with a bubble in lactose. (The sugar medium was prepared by the *B. coli* method and readings were made every day for three days.) The amount of gas present represents a fair estimate of the amount of acidity also. The microörganism is aerobic and grows best at 37°C., although it grows from 8°C. to 45°C. It is most usually a bipolar, diplo-bacillus, but sometimes appears like a coccus or sometimes has a diphtheroid form. It is gram-negative and non-acid fast.

L82: Large caseous abscess at the local site measuring 2 x 2 x 0.5 cm., composed of yellowish-gray necrotic material. Tissues around are markedly inflamed. The retroperitoneal lymph nodes are slightly enlarged. There is 5 cc. of serosanguineous fluid in the peritoneal cavity. The spleen is twice normal size, and is dotted with numerous grayish points, about 1 mm. in diameter and about 2 mm. apart, similar to the condition found in L19. The liver is grayish-yellow with a pinkish cast. There are a few yellow patches, measuring 1 mm. in diameter and with a pink border. A distinct fibrinous deposit is found on the upper side of the liver. The kidneys are pale yellowish-red. The adrenals are pale yellow and are slightly enlarged. The lungs are boggy and reddish. The hilum lymph nodes are enlarged. The substernal lymph nodes are also enlarged.

Microscopic findings: Are essentially the same as in the case of L19. (Figs. 1, 2, and 3.)

Bacteriology: The bacteriological findings vary from those of L19 in that there is a much greater activity of the microörganism. There is a more luxuriant growth, more gas and acid in sugar media, more acid clot and proteolysis of milk, slight indol reaction, etc. (Fig. 4.)

From a small bit of macerated spleen guinea pigs M15 and M16 were inoculated, and death resulted in much the same manner as in the others. M17 and M18 were each given an injection of liver with the same results.

In order to make sure that these deaths were not caused by an epidemic due to microörganisms in the stock, the whole procedure was repeated by placing a concentration of 1–2000 over another suspension of tubercle bacilli that responded to the ordinary tests for purity, and by injecting these into guinea pigs after a 30-day interval. The whole bouillon suspension was made up to 5 cc., and 0.5 cc. injected into guinea pig M8 subcutaneously, and 0.05 cc. into

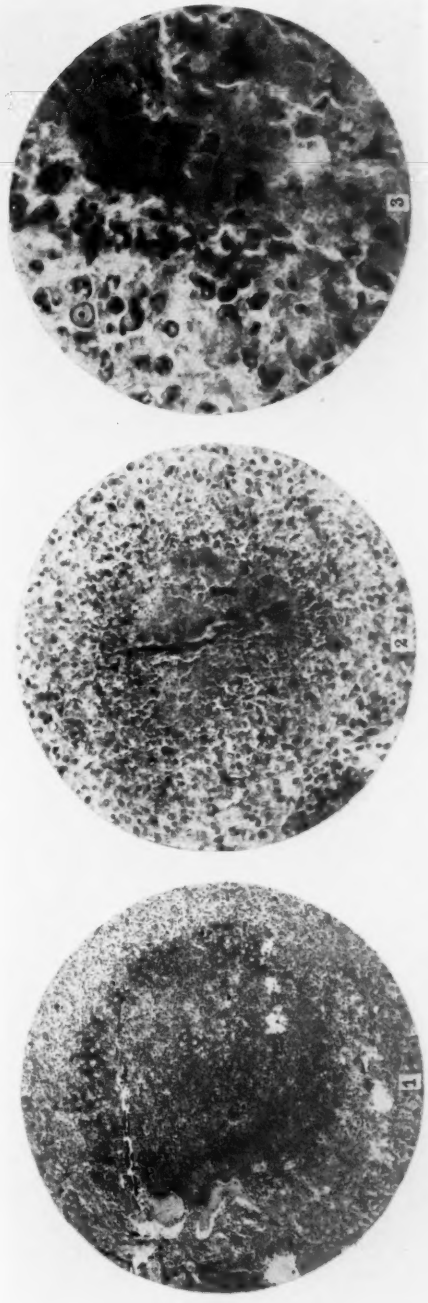

FIG. 1. Low-power drawing of tubercle-like formation in the adrenal gland of guinea pig L82. × 35
FIG. 2. Low-power drawing of tubercle-like formation in the spleen of guinea pig L82. × 140
FIG. 3. Oil-immersion photograph of border of lesion in spleen of guinea pig L82. × 700

guinea pig M10 on September 10, 1925. On September 18, 1925 M8 died of the usual septicemic condition. M10 was killed on October 27, 1925, and revealed the same type of lesions to a lesser degree. The spleen of M10 was macerated, and a small amount was injected into guinea pig N45, which died in 27 days, having enteritis, lymph-node enlargement (mesenteric and hilum), gelatinous pneumonia in the upper lobes, miliary abscesses in the liver, etc. This serial inoculation and repeated passage were done to see whether an acid-fast nature could be restored similar to that reported by Ferran (2). At no time, however, were we able to find acid-fast forms in these lesions. Acid-fast stains, gram stains and methylene-blue stains were made on direct smears from the liver, spleen, and sometimes the lungs, blood, adrenals and kidneys. Although

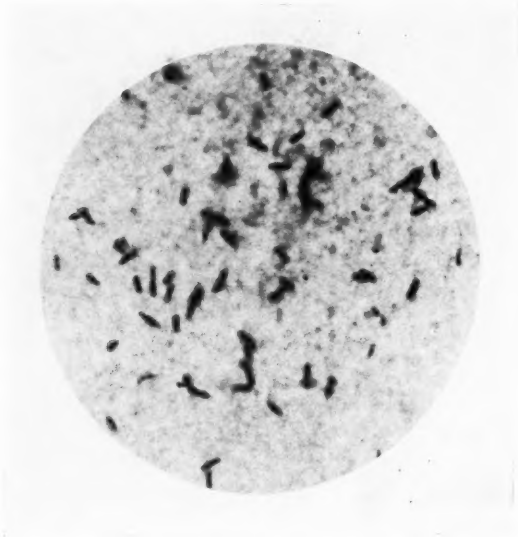

FIG. 4. Three-day milk culture from the spleen of guinea pig L82. × 1200

the various microörganisms isolated from the different animals were quite variable and assumed various morphological and cultural characteristics, there was not the least evidence of a reversion to the acid-fast form. A few of the microörganisms isolated from the various animals were studied in detail and the results are summarized in table 1.

ANALYSIS OF TABLE 1

A culture from guinea pig M18 (no. 55), which was inoculated from L82 (no. 29), differed from L82 only in that the milk was rendered alkaline in ten days with no clot, but with a gradual proteolysis and clearing that took place

TABLE 1

CULTURE NUMBER	SOURCE	INDOL	MILK			DEXTROSE*	LACTOSE	SUCROSE	GALACTOSE	LEVULOSE	DULCITE	INULIN	SALICIN	MANNITE
			Acid	Clot in days	Proteolysis									
				days										
38	A20	∓	++	1	+	++++ 6.5/20	++ 8.5/65	++ 8.5/28	alk. 2.5/0	++ 6.0/25	++++ 8.5/10	0 0.5/0	++++ 7.5/12	++++ 6.0/10
35	A21	++	+	2	+	++++ 3.5/30	alk. B	+++ 2.0/0	+++ 1.5/0	++ B	0 B	+ B	+ B	0 B
34	A18	∓	+++	1	++++	++++ 1.5/0	+++ 1.0/0	++++ 2.5/0	++++ 1.0/0	++++ 2.0/0	alk. 0.5/0	alk. 1.0/0	++++ 4.2/35	++++ 6.0/33
36	L21 from A18	++++	+	3	+	+ 0	∓ 0	+ 0	++ 0	++ 0	0 0	∓ 0	∓ 0	+ 0
33	L65 from A18	∓	+++	2	+++	++++ 8.0/34	+++ 2.8/0	++++ 8.3/34	+++ 8.3/33	++++ 8.5/34	+ 1.3/0	+ 1.5/0	++++ 8.2/35	++++ 9.5/35
32	L26 from A18	−	+++	2	+	++++ 7.5/40	+++ 4.5/30	++++ 8.5/13	+++ 6.5/40	++++ 4.5/0	0 1.5/0	0 1.5/0	++++ 4.5/8	++++ 8.5/12
8	L19 from A19	−	++	0	0	++++ 2.3/10	++ B	∓ 0	++++ 0.8/0	++++ 4.2/35	++++ 0.6/0	∓ 0	∓ 0	++++ 1.5/0
29	L82 from L19	+	++++	1	+++	++++ 7.0/33	++++ 9.0/30	++ 0.3/0	++++ 7.5/32	++++ 8.0/33	+++ 7.2/32	++ B	++ B	++ 1.0/0
55	M18 from L82	−	+	0	alk.	++++ 6.7/30	+++ 7.0/32	alk. B	++++ 4.7/26	++++ 6.3/33	+++ 6.5/15	0 B	alk. B	++++ 6.5/30

* The numerator signifies cm. of gas, the denominator percentage CO_2, the plus signs the degree of acidity.

mostly at the top of the tube. The other cultural characteristics are almost identical to those of L82 (no. 29). The next four cultures are all from guinea pig A18, directly or by passage through other animals. Culture no. 34 from A18 is a microörganism with only a mild degree of activity and producing only a small amount of gas in the sugars but a marked proteolytic activity in milk. Cultures no. 32 and 33 from guinea pigs L26 and L65, respectively, were almost identical, but differed from no. 34 by showing more activity in the sugars, although this activity paralleled the activity of no. 34 rather closely. Culture no. 36 was quite different from the other three, there being no gas in the sugars with only slight acidity. There was a strong indol reaction. This microörganism was more virulent than any of the others. The animals died quickly and the peritoneal cavity was inflated with gas. Culture no. 35 resembled no. 36 except that there was a slight amount of gas in most of the sugars and there was not so much indol. Culture no. 38 resembled no. 29 in many respects, although there were variations from this, there being more alkali in the milk, and gas in salicin medium.

Because of the fact that the tubercle bacilli used in the preceding experiments were of low virulence and uncertain purity (although the usual tests for purity were satisfactory), new cultures were prepared in which great precaution was used to eliminate contamination. Some highly virulent strains were obtained. One, from patient no. 20,676 was placed under a concentration of 1–2000 sanocrysin, and in thirty days 0.1 and 0.9 cc. of the emulsion were inoculated intraperitoneally into two guinea pigs, respectively. Both died of tuberculosis; the one receiving the larger dose died in 31 days and is worthy of description. There were numerous fine tubercles over the peritoneum, measuring less than a millimetre in diameter. The testicles were completely destroyed. Only the epididymis remained. The spleen was enlarged twofold. The liver was dark red, with numerous yellowish abscesses over the surface, measuring 2 to 3 mm. in diameter. The lungs had a gelatinous pneumonia in the lower lobes. The hilum lymph nodes were moderately enlarged. A few acid-fast bacilli were found in most of the organs. A greater number of partially acid-fast bacilli were found. In all the organs, especially in the remnants of the testicles, were large groups of cocci that were gram-positive and pathogenic for guinea pigs, producing a lymph-node hypertrophy and death of the animals in about 30 days.

DISCUSSION AND CONCLUSIONS

There appears to be a difference in results between the virulent and the avirulent cultures. From the avirulent cultures there seemed to develop a form of microörganism that produced in guinea pigs many characteristics of tuberculosis, yet after many passages no typical acid-

fast microörganisms were ever observed, while from the virulent culture an atypical tuberculosis with a few acid-fast bacilli appeared following the first injection. Along with the tubercle bacilli appeared a pathogenic coccus the rôle of which is yet undetermined.

It can be stated definitely that sanocrysin is not completely bactericidal within a period varying from 30 to 78 days, and that even after 78 days there are microörganisms (possibly mutants of the tubercle bacillus) that are still quite virulent for guinea pigs. Whether such microörganisms play a rôle in therapy of human patients is still a question, but it must be granted that the possibility warrants discretion and care in treatment. We have shown previously that sanocrysin inhibits the growth of the tubercle bacillus *in vitro* in concentrations as low as 1–1,000,000, confirming Moellgaard's first report (3). A distinction must be made, however, between the inhibition in culture media and inhibition in the living body, where the respective environments are in no sense the same. It must also be pointed out that different strains of tubercle bacilli react differently, some growing well on ordinary media, while others do not grow at all, or only after great care during the first few generations. We can therefore make no statements regarding the effect of sanocrysin on tubercle bacilli that do not grow well on artificial media. There is the possibility that the good results reported have been chiefly due to the effect on this group of microorganisms that are detrimentally influenced by foreign substances, including sanocrysin. Then there is still the possibility that only part of the microörganisms are affected, leaving enough to produce the tuberculosis in the animals, yet killing enough bacilli to have some value in the treatment of the disease. However this may be, sanocrysin does not kill all the germs outright, or even in a month's time. The more the drug is studied, the more it appears that the favorable effect is due as much or more to the ability of the patient "to react" than to the specific effect on the parasite. This reaction may be due primarily to the stimulating effect on the young reticulo-endothelium, and secondarily to the power of such metallic substances to increase oxidation by catalytic action.

SUMMARY

1. The effect of long exposure to sanocrysin on avirulent and virulent tubercle bacilli has been reported.

2. A concentration of 1–2,000 does not kill all virulent tubercle bacilli in 30 days. In avirulent cultures, after 78 days' exposure, peculiar microörganisms are reported that produce a "tuberculoid" condition in guinea pigs.

3. The pathological properties (in guinea pigs) and the bacteriology of some of these cultures are given.

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THE EFFECT OF INJECTIONS OF SANOCRYSIN ON NORMAL AND TUBERCULOUS DOGS

Part II: On Tuberculous Dogs[1,2]

LILLIAN EICHELBERGER AND K. LUCILLE McCLUSKEY

An earlier paper (1) reported the results of intravenous injections of sodium-auro-thio-sulphate (*Sanocrysin*) on normal dogs with respect to urinary changes, the elimination of gold and the latter's distribution in the various organs. The present work constitutes a parallel study on tuberculous dogs.

PROCEDURE AND TECHNIQUE

In an attempt to duplicate as nearly as possible the conditions of the former study, a group of four normal male dogs, weighing from 13 to 15 k., was used. They were maintained for 10 days on a dietary which was the same as that given the nontuberculous dogs. Each dog then received an intravenous injection of 0.5 mgm. per kilo body-weight of bovine tubercle bacilli, strain 191. The bacilli were emulsified in sterile physiological salt solution for injection. Fifteen days after inoculation, twenty-four-hour specimens of urine were collected for six consecutive days and analyzed for chlorides, urea, ammonia, creatinine and physical properties. The technique, number of, and interval between injections of sanocrysin,[3] amounts injected, and all chemical methods were the same as in the previous work.

To study the distribution and deposition of gold in the organs at different intervals, the dogs were necropsied as follows: Dog TM was killed 35 days after the third injection of sanocrysin and 5 days after the disappearance of gold from the urine. Dogs MM and PM were each given a fourth injection of 40 mgm. per kilo body-weight of sanocrysin

[1] From the Research Laboratories, Chemical Department, of the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

[2] Read at the Twenty-Second Annual Meeting of the National Tuberculosis Association, Washington, D. C., October 5, 1926.

[3] The sodium-auro-thio-sulphate used in this experimental work was prepared by the authors (2).

and necropsied 2½ hours and 24 hours, respectively, after the injection. Control dog HM was killed at this time. Sections of all organs were taken for histological study. Examination of the slides was made by Dr. Paul R. Cannon, Assistant Professor of Pathology, University of Chicago, whose report is found in the protocols under *Histological Findings*.

PROTOCOL OF DOG PM

May 16, 1925: Weight: 14.65 k. Injected intravenously with 7.32 mgm. of bovine tubercle bacilli, strain 191, or 0.5 mgm. per kilo body-weight.

June 2–7, 1925: Quantitative chemical examinations were made on the 24-hour urine specimens.

June 8, 1925: Weight: 16.55 k. First injection of sanocrysin; dose, 331 mgm. (20 mgm. per kilo body-weight).

June 30, 1925: Weight: 16.798. Second injection of sanocrysin; dose, 504 mgm. (30 mgm. per kilo body-weight).

July 31, 1925: Weight: 16.165 k. Third injection of sanocrysin; dose, 646.6 mgm. (40 mgm. per kilo body-weight).

September 4, 1925: Weight: 16.308 k. Fourth injection of sanocrysin; dose 652 mgm. (40 mgm. per kilo body-weight).

September 5, 1925: Necropsied exactly 24 hours after the last injection of sanocrysin.

Observations

Weight (chart 1): The weight chart shows that from the time of inoculation with tubercle bacilli (May 16) until the second injection of sanocrysin (June 30) there was a steady gain in weight, amounting to 14.0 per cent. During the next month there was a loss of 3.9 per cent, followed by a slight increase of approximately 0.8 per cent.

Temperature: A slight increase of temperature up to 102.6° was observed during the first three weeks after inoculation. After that the temperature always varied from 101° to 101.7°, except after the injection of sanocrysin, when an increase from 0.5° to 0.9° was observed after each injection: 101.5° is considered the average normal temperature per rectum for the dog.

Urinary Findings (table 3 and chart 2): Changes in the urinary constituents are shown in table 3 and chart 2. It can be observed that there was a slight increase over the preinjection period of approximately 1 to 10 per cent in the urea excretion following injections of sanocrysin. There was a decided increase (37 to 54 per cent) in the chloride elimina-

TABLE 1

Percentage of gold recovered from the urine following sodium-auro-thio-sulphate injections

DAY	DOG MM						DOG PM						DOG TM					
	13.759 kgm.		14.212 kgm.		10.210 kgm.		16.55 kgm.		16.798 kgm.		16.165 kgm.		13.670 kgm.		13.970 kgm.		14.520 kgm.	
	First injection, 20 mgm. per kilo		Second injection, 30 mgm. per kilo		Third injection, 40 mgm. per kilo		First injection, 20 mgm. per kilo		Second injection, 30 mgm. per kilo		Third injection, 40 mgm. per kilo		First injection, 20 mgm. per kilo		Second injection, 30 mgm. per kilo		Third injection, 40 mgm. per kilo	
	Per cent per day	Total per cent	Per cent per day	Total per cent	Per cent per day	Total per cent	Per cent per day	Total per cent	Per cent per day	Total per cent	Per cent per day	Total per cent	Per cent per day	Total per cent	Per cent per day	Total per cent	Per cent per day	Total per cent
1	15.56	15.56	22.45	22.45	13.61	13.61	14.54	14.54	26.57	26.57	27.38	27.38	5.00	5.00	9.99	9.99	15.72	15.72
2	9.04	24.60	8.23	30.68	7.91	20.52	8.67	23.21	8.75	35.32	12.69	40.07	3.44	8.45	13.96	23.95	9.64	25.36
3			3.89	34.57	4.73	25.25	4.44	27.65	4.03	39.35	3.68	43.75			3.45	27.30	0.77	26.13
4	2.14	26.74	5.20	39.77	4.67	29.92	4.20	31.85	3.87	43.22	2.57	46.32	2.35	10.80	2.55	29.85		
5			2.32	42.09	3.41	33.33	2.42	34.27	2.81	46.03	1.32	47.64	2.52	14.32	1.15	31.00	1.34	27.47
6			0.88	42.97	2.60	35.93	2.27	36.54	0.95	46.98	1.56	49.20	1.37	15.69	1.60	32.60	3.18	30.65
7	1.75	28.49	2.82	45.79	2.68	38.61	1.70	38.24	2.17	49.15	1.37	50.57	1.66	17.35	0.77	33.37		
8	1.46	29.95	1.07	46.86	0.97	39.58	2.83	41.07	1.17	50.32	1.32	51.89	1.66	19.01	1.27	34.64	1.84	32.49
9	1.85	31.80	2.26	49 12	0.66	40.24	2.83	43.90	1.11	51.43	2.77	54.66	1.37	20.38	1.27	35.91	1.59	34.08
10	1.36	33.16			0.06	40.30	1.86	45.76			0.99	55.65	1.95	22.33			1.15	35.23
11	2.33	35.49			0.97	41.27	3.15	48.91			0.58	56.23	2.44	24.77			0.83	36.06
12											0.95	57.18						
13	3.70	39.19	2.58	51.70	1.05	42.32	2.67	51.58	1.32	52.75			3.22	27.99	2.04	37.95	2.76	38.82
16			2.19	53.89											2.36	40.31		
17					2.55	44.87					1.41	58.59					1.15	39.97
18	8.75	47.94					5.66	57.24										
20									2.87	55.62								
22					5.04	49.91					2.52	61.11					3.73	43.70
27			3.07	56.96	1.57	51.48					2.44	63.55			1.92	42.23	1.38	45.08
31																	2.62	47.70

tion. The creatinine and ammonia were fairly constant, with the exception of the ammonia excretion following the first sanocrysin injection. The urine-volume curve shows a drop following the first and second injections, but rises after the third injection. In general, the curve shows a condition of oliguria throughout the experiment.

Elimination (tables 1 and 2): The percentage of the injected gold recovered in the urine was between 58.62 and 63.55 per cent; 36.54 to 49.2 per cent was eliminated during the first 6 days, leaving an average of about 15 per cent recovered after the sixth day. The period of elimination increased with increasing doses of sanocrysin, and lasted from 18 to 27 days.

TABLE 2

A summary of the percentages of gold recovered from the urine after injections of sodium-aurothio-sulphate

	DOG MM			DOG PM			DOG TM		
	Total per cent recovered	Percentage recovered for first 6 days	Percentage recovered after 6th day	Total percentage recovered	Percentage recovered for first 6 days	Percentage recovered after 6th day	Total percentage recovered	Percentage recovered for first 6 days	Percentage recovered after 6th day
First injection, 20 mgm. per kilo	47.94	26.74	21.20	57.24	36.54	20.70	27.99	15.69	12.30
Second injection, 30 mgm. per kilo	56.96	42.97	13.99	55.62	46.98	8.64	42.23	32.60	9.63
Third injection, 40 mgm. per kilo	51.48	35.93	15.55	63.55	49.20	14.35	47.70	30.65	17.05
Average	52.13	35.21	16.91	58.80	44.24	14.56	39.31	26.31	12.99

Distribution of Gold in the Organs (tables 4 and 5): There appears to be quite a definite distribution of gold in the organs of animals subjected to similar conditions. This is best observed by comparison of the findings of this dog with dog SM_2 of the previous study. Both dogs were necropsied 24 hours after the fourth injection of sanocrysin. The results show that 36 per cent of gold of the last injection was found in the organs of dog PM, and that 18 per cent was eliminated during the 24 hours in the urine, making a total of 54 per cent. Dog SM_2 had 37 per cent of the gold from the last injection in the organs and a urinary elimination of 25 per cent during the 24 hours, making a total of 62 per cent. The concentration of the gold found in the kidneys, liver and spleen of these

TABLE 3

Urinary findings before and after the injection of sodium-auro-thio-sulphate

PERIOD	VOLUME		NaCl		UREA N_2		AMMONIA N_2		CREATININE	
	Cubic centimetres	DN* per cent	Grams	DN per cent	Grams	DN per cent	Grams	DN per cent	Grams	DN per cent
Dog HM (control)										
6 days before first injection	4345		13.74		52.72		1.97		4.04	
6 days after first injection	2887	−33.5								
6 days after second injection	4777	+9.9	11.92	−13.2	55.49	+5.2	2.84	+44.1	2.92	−27.7
6 days after third injection	4160	−4.2	16.55	+21.1	42.40	−19.8	2.61	+32.3	2.58	−36.1
Dog MM										
6 days before first injection	3000		14.06		55.50		1.77		3.06	
6 days after first injection	2325	−22.5	9.32	−33.7	33.48	−39.7	1.79	+1.1	2.15	−29.7
6 days after second injection	5205	+73.5	13.59	−3.3	51.29	−7.6	1.58	−10.7	3.24	+6.0
6 days after third injection	2500	−16.6	4.24	−69.8	29.31	−47.2	1.26	−28.8	1.71	−44.1
Dog PM										
6 days before first injection	5520		11.69		63.40		3.31		3.91	
6 days after first injection	4970	−9.9	16.04	+37.2	64.0	+0.9	2.58	−22.0	3.84	−1.7
6 days after second injection	5290	−4.1	16.48	+40.9	66.49	+4.8	3.41	+3.0	3.91	0.0
6 days after third injection	5055	−8.4	18.03	+54.2	69.25	+9.2	3.49	+5.4	4.13	+5.6
Dog TM										
6 days before first injection	1800		9.19		44.78		1.09		2.42	
6 days after first injection	2470	+37.2	10.33	+12.4	43.24	−3.4	1.48	+35.8	2.28	−5.7
6 days after second injection	3375	+87.5	14.21	+54.6	38.59	−14.8	3.84	+252.2	1.23	−49.1
6 days after third injection	3192	+77.3	10.05	+9.4	28.66	−35.9	2.46	+125.6	1.44	−40.5

* DN per cent = deviation from preinjection period in per cent.

TABLE 4

Distribution of gold in organs after sodium-auro-thio-sulphate injections

ORGAN	DOG TM			DOG MM			DOG PM		
	Necropsied 34 days after third injection and 5 days after the diappearance of gold from the urine			Necropsied 2 and ½ hours after fourth injection (101.5 mgm. of gold)			Necropsied 24 hours after fourth injection (242.88 mgm. of gold)		
	Weight of organ	Mgm. of gold to gm. of organ	Mgm. of gold found	Weight of organ	Mgm. of gold to gm. of organ	Mgm. of gold found	Weight of organ	Mgm. of gold to gm. of organ	Mgm. of gold found
	grams			*grams*			*grams*		
Kidneys	112.0	1:15	7.6	81.0	1:6	12.6	81.7	1:1.4	57.6
Spleen	40.5	1:18	2.2	17.0	1:9	1.9	31.0	1:52	0.6
Liver	750.0	1:227	3.3	620.0	1:194	3.2	552.0	1:38	14.27
Pancreas	9.8	1:3	3.2	22.0	1:22	1.0	31.8	1:18	1.8
Bladder				13.2	1:10	1.3	15.5	1:2	5.0
Lungs	117.0	1:78	1.5	103.5	1:69	1.5	115.3	1:23	5.0
Adrenals	3.0	0:1	0.0	3.5	1:2	1.6	2.0	Negative	
Heart	109.5	1:122	0.9	53.0	1:53	1.0	114.5	1:57	2.0
Total			18.7			24.1			86.27
Urine between fourth injection and necropsy						12.0			44.1
Sum total			18.7			36.1			130.37

TABLE 5

Comparison of the gold content of organs of tuberculous (TB) and nontuberculous (NTB) dogs

ORGAN	DOGS AUTOPSIED 46 AND 34 DAYS RESPECTIVELY AFTER THIRD INJECTION		DOGS AUTOPSIED 2½ HOURS AFTER FOURTH INJECTION		DOGS AUTOPSIED 24 HOURS AFTER THIRD INJECTION	
	NTB Dog BuM_3, mgm. of gold	TB Dog Tm, mgm. of gold	NTB Dog BM_4, mgm. of gold	TB Dog MM, mgm. of gold	NTB Dog SM_2, mgm. of gold	TB Dog PM, mgm. of gold
Kidney	3.4	7.6	40.3	12.6	44.2	57.6
Liver	9.5	3.3	14.4	3.2	11.7	14.27
Spleen	1.3	2.2	0.8	1.9	1.1	0.6
Lungs	0.9	1.5	1.5	1.5	1.9	5.0
Heart	1.1	0.9	Did not determine	1.0	Negative	2.0
Pancreas	Trace	3.2	2.6	1.0	1.3	1.8
Bladder	Trace	Did not determine	1.0	1.3	0.8	5.0
Adrenals	Trace	Negative	Did not determine	1.6	1.9	Negative
Total	16.2	18.7	60.6	24.1	62.2	86.27
Total mgm. of injected gold	480.0	476.2	567.0	516.4	577.9	797.9
Per cent recovered	3.38	3.92	10.68	4.67	10.76	10.81

dogs was practically the same, and decreased in the order of the organs mentioned.

Histological Findings: Liver, myocardium and pancreas are normal. Lungs show slight simple edema. Spleen has trabeculae markedly hyalinized; is otherwise normal. Kidney: In certain areas of the kidney there are localizations of small lymphocytes and epithelioid cells in the cortex. In these regions the glomerular capsules are greatly thickened and hyalinized, and the tufts themselves are obliterated. The process resembles early tuberculosis, although there are no caseation and no giant cells.

PROTOCOL OF DOG TM

May 16, 1925: Weight: 13.067 k. Injected intravenously with 6.53 mgm. of bovine tubercle bacilli, strain 191, or 0.5 mgm. per kilo body-weight.

June 2–7, 1925: Quantitative chemical examinations were made on 24-hour specimens of urine.

June 8, 1925: Weight: 13.670 k. First injection of sanocrysin; dose, 273.5 mgm. or 20 mgm. per kilo.

June 30, 1925: Weight: 13.970 k. Second injection of sanocrysin; dose, 419.0 mgm., or 30 mgm. per kilo.

July 31, 1925: Weight: 14.520 k. Third injection of sanocrysin; dose, 580.8 mgm., or 40 mgm. per kilo.

September 4, 1925: Weight: 15.061 k. Necropsied 34 days after the third injection and 5 days after the urine was free from gold.

Observations

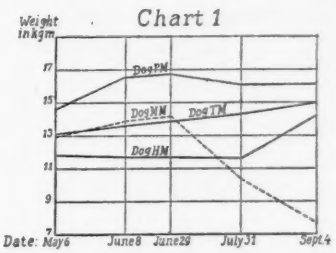
Weight (chart 1): The weight-curve indicates a steady gain of 15.2 per cent during the experimental period.

Temperature: The normal rectal temperature for this dog was 101.4°. A number of afternoons during the experimental period a rise of temperature from 102.2° to 102.4° was recorded. The elevation was present at intervals between June 1 and June 29. After that time there was a return to normal.

Urinary Findings (table 3 and chart 3): A comparison of the chemical findings on the urine six days before the injection of sanocrysin with the six days following each subsequent injection shows the following deviations: An increase in chlorides from 9.4 to 54.6 per cent, an increase in ammonia from 125.6 to 252.2 per cent, a decrease in urea from 3.4 to 35.9 per cent, and a decrease in creatinine from 5.7 to 40.5 per cent.

The urine-volume curve is characterized by a gradual increase in the volume of urine during the periods following the first and second injections of sanocrysin. Immediately following the third injection there was an abrupt drop in the curve.

Elimination (tables 1 and 2): The 24-hour specimens of urine were



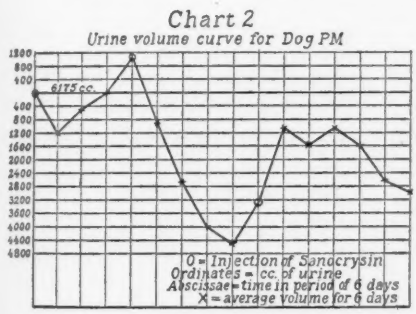


Chart 2
Urine volume curve for Dog PM
6175 cc.
0 = Injection of Sanocrysin
Ordinates = cc. of urine
Abscissae = time in period of 6 days
X = average volume for 6 days

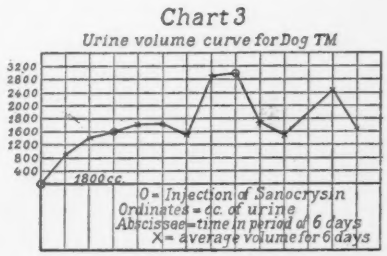


Chart 3
Urine volume curve for Dog TM
1800 cc.
0 = Injection of Sanocrysin
Ordinates = cc. of urine
Abscissae = time in period of 6 days
X = average volume for 6 days

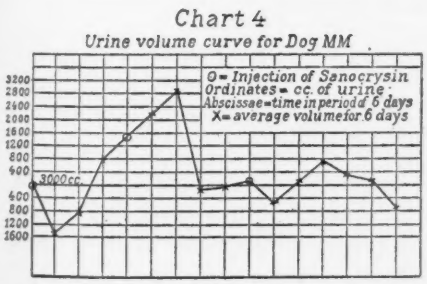


Chart 4
Urine volume curve for Dog MM
3000 cc.
0 = Injection of Sanocrysin
Ordinates = cc. of urine
Abscissae = time in period of 6 days
X = average volume for 6 days

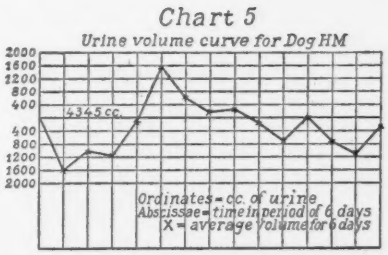


Chart 5
Urine volume curve for Dog HM
4345 cc.
Ordinates = cc. of urine
Abscissae = time in period of 6 days
X = average volume for 6 days

analyzed daily for gold. After the first injection 27.99 per cent of the total gold injected was recovered, after the second injection 42.23 per cent, and after the third injection 47.70 per cent, thus making an average recovery of 39.31 per cent from the three injections. The gold was eliminated by the kidneys in from 18 to 30 days, the period of elimination depending upon the dosage of sanocrysin. The greater percentage of the

gold was eliminated during the first six days succeeding each injection. An average of the urinary elimination of gold from the three injections shows that 26.31 per cent was recovered during the first six days after the injection, and 12.99 per cent after the sixth day.

Distribution of Gold in the Organs (tables 4 and 5): The salient features in the distribution of gold in the organs of this dog were the high concentration of gold in the kidneys and spleen, and the low concentration in the liver. If a comparison is made of the tuberculous dog TM, which was necropsied 34 days after the third injection and 5 days after the urine was free from gold, with the normal dog BuM_3 which was killed 42 days after the third injection and 8 days after the urine was free from gold, the following points are most evident: The percentage recovery of the total gold injected from the organs in each of the normal and tuberculous dogs was 3.38 and 3.63 per cent, respectively, and the greatest proportion of gold in milligrams per gram weight of tissue was in the order of kidney, spleen and liver.

Histological Findings: Liver: Marked lymphocytic increase in perilobular areas. No tubercles seen. *Lung:* No marked evidence of tuberculosis. Much pulmonary edema. There were a few small collections of lymphocytes and epithelioid cells, which may well be very early tuberculosis. The spleen, adrenal, pancreas, myocardium and kidneys were apparently normal.

PROTOCOL OF DOG MM

May 16, 1925: Weight: 13.015 k. Injected intravenously with 6.5 mgm. of bovine tubercle bacilli, strain 191, or 0.5 mgm. per kilo body-weight.

June 2–7, 1925: Quantitative chemical examinations were made on the 24-hour specimens of urine.

June 8, 1925: Weight: 13.759 k. First injection of sanocrysin; dose, 275 mgm. (20 mgm. per kilo body-weight).

June 30, 1925: Weight: 14.212 k. Second sanocrysin injection; dose, 426.3 mgm. (30 mgm. per kilo body-weight).

July 31, 1925: Weight: 10.210 k. Third sanocrysin injection; dose, 408.4 mgm. (40 mgm. per kilo body-weight).

September 4, 1925: Weight: 7.838 k. Fourth injection of sanocrysin; dose, 313 mgm. (40 mgm. per kilo body-weight).

Observations

Weight (chart 1): There was a good and steady gain in weight for the first two months following the inoculation with tubercle bacilli, as shown

in the weight-curve. On July 10th the dog did not consume all of its regular diet, and from then on its condition became rapidly worse. At times only a cup or two of milk was taken per day. During the last month and a half, this dog lost 45 per cent of its weight, and became so emaciated that it was unable to stand.

Temperature: For two weeks following inoculation with tubercle bacilli, there was observed a temperature of about 102.2°. A fever reaction was observed about 6 hours after the first injection of sanocrysin, but the temperature returned to normal on the following day. From the thirty-eighth day after inoculation until the animal was necropsied (the one hundred and eleventh day) the temperature stood between 102.1° and 102.8° with one exception, on the forty-fourth day, when it was 103.7°.

Urinary Findings (table 3 and chart 4): Only the urinary findings following the first two injection periods can be used for comparative study, since the dog was not consuming the regular measured dietary of the preinjection period after July 10th. Comparison of the results of the first two injection periods with the preinjection sanocrysin period shows that there was a decided decrease in the volume, chlorides, urea and creatinine after the first injection of sanocrysin. Following the second injection there was a return to the condition as found previous to sanocrysin injection, as indicated by the values for chlorides, urea and creatinine. During this time there was a marked increase in the volume of urine, possibly the result of a beginning active tuberculous process. After the third injection of sanocrysin there was a decided decrease in the elimination of creatinine and ammonia, two constituents presumably altered little by dietary changes.

Elimination (tables 1 and 2): The amount of gold recovered in the urine during the three injection periods varied from 47.95 to 56.96 per cent. From 26.74 to 42.97 per cent of gold was recovered during the first 6 days, with an average of 17 per cent recovery after the sixth day. The period of elimination following the first injection of sanocrysin was 18 days. The second and third periods were each 27 days.

Distribution of Gold in the Organs (tables 4 and 5): Two and one-half hours after a fourth injection of 313 mgm. of sanocrysin, which is equivalent to 101.5 mgm. of gold, the dog was necropsied. If a comparison is made between the findings of this dog with the tuberculous dog TM and with the nontuberculous dog BM_4 of the earlier study, the outstanding observation is that two and one-half hours after the fourth injection there appeared to be no increase in the gold in the organs of dog MM from

this last injection of sanocrysin, except perhaps a slight increase in the kidney. The slow diffusion of gold was undoubtedly due to the extreme pathological changes in this dog.

Histological Findings: The pancreas, spleen, myocardium and adrenal appear to be essentially normal. *Lungs:* Numerous small collections of lymphocytes, epithelioid cells and fibroblasts. No caseation or giant cells, but very early tubercles. *Liver:* Infiltration of macrophages and lymphocytes, so extensive in the periportal and perilobular areas as to almost obliterate the liver cords. It is a very widespread tuberculous reaction. Sections, stained with Gabbett's stain, picric acid and methylene-blue counterstain, showed several tubercle bacilli per field.

PROTOCOL OF DOG HM (CONTROL)

May 16, 1925: Weight: 13.765 k. Injected with 6.88 mgm. of bovine tubercle bacilli, strain 191, or 0.5 mgm. per kilo body-weight.

June 2–7, 1925: Quantitative chemical examinations were made on 24-hour specimens of urine.

June 29 to July 5, 1925: Weight: 13.658 k. Quantitative chemical examinations were made on 24-hour specimens of urine.

July 31 to August 5, 1925: Weight: 13.589 k. Quantitative chemical examinations were made on 24-hour specimens of urine.

September 2, 1925: Weight: 14.287 k. Necropsied.

Observations

Weight (chart 1): The weight-curve shows a slight decrease in value until the latter part of the experimental period when a slight increase is noticed on September 2nd.

Temperature: The normal rectal temperature for this dog was 101.4°. Between the time of inoculation with tubercle bacilli and August 14th, the dog had a febrile reaction varying from 102.6° to 104.7° with one exception. On June 23rd the temperature was 101.6°. After August 14th it remained within normal limits.

Urinary Findings (table 3 and chart 5): The urine from the control animal was analyzed at the same time as that from the dogs injected with sanocrysin. The only definite and consistent observations made were a large increase in the ammonia (32 to 44 per cent) and a simultaneous decrease in creatinine (28 to 36 per cent). The chlorides and urea varied somewhat, a decrease in one constituent being accompanied by an increase in the other and vice versa. Chart 5 shows a fluctuation

in the urine-volume following intravenous inoculation with tubercle bacilli. There appears to be a decrease at first, followed by an increase, and later a period of less marked variation. That these decided fluctuations are due to the tubercle bacilli cannot be determined at this time.

Histological Findings: Kidneys. One area of the cortex, and extending into the medulla, is densely infiltrated with round cells and epithelioid cells. No giant cells are seen. In this area the glomeruli show pyknotic nuclei. There is one localized area of round cells and epithelioid cells, which is apparently a tubercle. *Spleen:* Marked hyalinization of trabeculae and blood-vessel walls; otherwise normal. *Lungs:* Moderate pulmonary edema and hemorrhage. The myocardium, adrenal, liver and pancreas are apparently normal.

Elimination of Gold in the Urine: The daily elimination of gold through the kidney is reported in table 1 and is summarized in table 2. The greatest daily excretion of gold occurred during the first 24 hours. If these findings are contrasted with those in the nontuberculous dogs, the most salient points to be observed are the total recovery, and the recovery after the sixth day. The total recovery of gold in the urine from the first injection of the nontuberculous dogs varied between 55.91 and 61.53 per cent, while the tuberculous dogs eliminated from 27.99 to 57.24 per cent. Following the second injection, the elimination of gold was 57.55 to 71.56 per cent for the nontuberculous dogs, and 42.23 to 56.96 per cent for the tuberculous dogs. After the third injection 48 to 68.26 per cent of gold was recovered from the nontuberculous dogs and 47.70 to 63.55 per cent from the tuberculous dogs. The amount recovered after the sixth day for the nontuberculous dogs varied from 10.59 to 12.50 per cent, while the tuberculous dogs eliminated from 13 to 17 per cent.

It can be observed in each instance that the total percentage recovery of gold from the tuberculous dogs is less by about 10 per cent than for the normal dogs, and that the amount eliminated after the sixth day was approximately 4 per cent greater for the tuberculous than the nontuberculous dogs. The coexistence of a lower total recovery of gold and a higher recovery after the sixth day, together with the findings of approximately the same distribution of gold in the organs, suggests a retention, due possibly to a slower rate of diffusion of sanocrysin in the tissues of the tuberculous animals, or to a lessened ability of the kidney to eliminate.

Urinary Findings: The effect of the injection of sanocrysin on the

urinary findings of the tuberculous dogs varied somewhat from the effects noted on the normal dogs. This difference may be the result of two opposing forces, namely, tuberculosis and sanocrysin. Usually the most outstanding features were a decrease in creatinine, an increase in ammonia and an increase in chlorides. The tendency toward acidosis which accompanies tuberculosis may be offered as an explanation for the increase of ammonia. Data in the literature on urinary changes in tuberculosis are not sufficient and conclusive to warrant a definite opinion at this time. Slight traces of albumin in the urine were observed throughout the experimental period in both the control and the animals that received sanocrysin.

Distribution of Gold in the Organs: The amount of gold found in the organs after sanocrysin injections shows that a certain specificity exists between gold and animal tissues. The concentration usually is found to be in the order of the kidney, liver, and spleen, if examination be made within 24 hours after an injection. When the interval between injection and necropsy was either 34 or 46 days, the concentration of gold was found to be greatest in the order of kidney, spleen and liver.

From table 5 it can be observed that the interval of time after an injection does not appear to alter the actual amount of gold found in the spleen of all dogs. The limits of variation were 0.6–2.2 mgm. per spleen, the smallest amount being found in the tuberculous dog, which had received the largest quantity of gold and which was necropsied *only* 24 hours after the last sanocrysin administration, while the greatest amount was found in the tuberculous dog autopsied 34 days after the last injection. In the majority of instances, the deposition of gold in the pancreas was greater than in the spleen, while the amount found in the heart and lungs was approximately constant for all dogs.

These observations are not in agreement with the findings of DeWitt on the distribution of gold in animal tissues following *Aurocantan* injection. This investigator states that gold seems to select the spleen by preference, and that sometimes the kidney and sometimes the liver comes second in gold concentration. That the organs have a selective preference for different metals has been proved by Huber (4), Blyth (5), Aikins and Corper (6), Glaister (7), Bulmer (8) and others. A summary of their findings indicates that copper, zinc, antimony and mercury are generally deposited in the liver much more than in the other organs. The spleen usually contains none or mere traces. Arsenic is usually distributed in high concentration in the liver very shortly after injection,

while the lung maintains a high arsenic content over a period of at least several days.

From table 5 it will be seen that there is no marked difference in the amount of gold deposited in the organs of the tuberculous and the nontuberculous dogs. From dogs TM and BuM_3, necropsied at similar times, the amount of gold recovered from the organs was 3.92 and 3.38 per cent of the total gold injected, while organs from dogs PM and SM_2, which were necrospied 24 hours after a fourth injection of sanocrysin, contained 10.81 and 10.76 per cent of the total amount of gold injected.

These results are in accord with the observation of DeWitt (3) that there is no marked difference between the deposition of gold in tuberculous and nontuberculous animals (guinea pig). This suggests that, at least in early tuberculosis, there is no specific affinity of the gold for tuberculous tissues.

SUMMARY

1. In tuberculous dogs, sodium-auro-thio-sulphate (sanocrysin) is eliminated principally through the urinary tract over a period of from 18 to 30 days.

2. The percentage of gold recovered from the urine of tuberculous dogs varied from 39 to 59 per cent, or an average of 50 per cent. This represents 10 per cent less than the average recovered from nontuberculous dogs.

3. The urinary findings were neither consistent nor in agreement with the observations made on nontuberculous dogs. This difference may be due to the presence of two simultaneous stimuli, namely, sanocrysin and tubercle bacilli.

4. A slight fever reaction was observed in most cases after intravenous injections of sanocrysin in tuberculous dogs.

5. The salient features in the distribution of gold in the organs following intravenous injections of sanocrysin are: A high concentration of gold in the kidney, and also in the liver shortly after injection; the relatively small amount of gold found in the spleen at any time; a usually greater deposition of gold in the pancreas than in the spleen; and a small but fairly consistent amount in the lungs and the heart.

The authors wish to express their indebtedness to Dr. Cannon for his contribution on the histological studies.

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AN EXPLANATION OF THE THERAPEUTIC ACTION OF OLEUM JECORIS[1]

G. PLATONOV

Codliver oil plays an important rôle in the treatment of tuberculosis. Up to now, however, there has been no scientific basis for its use. The mechanism of its healing effect has been attributed partly to the facility with which it is emulsified and assimilated because of its high content of low-melting neutral fats, and partly to its constituent vitamines. Yet it is doubtful whether the variable effect of codliver-oil treatment is due merely to the factors mentioned, for a number of other fats, such as butter, have all the above-mentioned properties yet lack the therapeutic efficiency of codliver oil. Some other explanation must be sought.

With that aim in view, workers have been lately attempting to determine the active fraction of codliver oil and extract it for therapeutic use in concentrated form. Thus, several American and English authors have obtained fatty acids of the unsaturated series to which the curative power of codliver oil has been ascribed (Tewkesbury, Power). Some derivatives of these fatty acids have been tested by the above-mentioned authors on patients with good results. These attempts are, however, far from being successfully completed, owing chiefly to a great deal of empiricism displayed in the use of these valuable preparations. Being inclined to attribute the healing virtue of *Oleum jecoris* to its unsaturated fatty components, I am endeavoring to determine the scientific principles of their use. In this effort, it is first necessary to mention the literature characterizing the immuno-biological rôle of unsaturated lipoids.

Thus, the study of the chemical nature of antibodies has shown their relation to unsaturated lipoids (complement, haemolysins, etc.). Owing to the absence of an adequate microchemical method, we are at present unable to follow the variation of the lipoid content of antibodies in the blood serum of tuberculosis patients. But another, though coarser, method shows the active part played by the unsaturated lipoids in the

[1] From the Tuberculosis Institute, People's Commissariat of Public Health, Moscow, Russia, Professor Dr. Vorobjev, Director.

struggle of the body against tuberculosis. This method is that of comparing the qualitative and quantitative analyses of the organs of normal and tuberculous animals (Grinev, Kondratovitsh, Palma). Since Palma's work is of special interest in this respect, I shall discuss it at some length.

Palma extracted unsaturated lipoids from the lymph nodes of normal and tuberculous cows. The lipoids obtained from the tuberculous cows were liquid, and their iodine-value was twice or even three times higher than that of the normal cows. This proves not only an accumulation, but also a qualitative change of the lipoids. Both the saturated and unsaturated fractions of the lipoids were investigated by the author as to their action upon tubercle bacilli. It was shown that the soaps of unsaturated lipoids acted bacteriolytically even in a concentration of 0.001 per cent. After 48 hours, the tubercle bacilli already lose their acid-fastness, and frequently break up into granules. The soaps of the saturated fraction acted more weakly.

Taking these facts into consideration, it can be asserted that a clear understanding of the pathogenesis and treatment of tuberculosis can be gained only by closely studying the biochemical processes in the affected organs, with special attention directed to the conditions under which unsaturated lipoids are formed in such organs. Of the great number of facts illustrating the biological importance of lipoids, I shall mention here only those which make it possible to ascribe the action of *Oleum jecoris* to its unsaturated lipoids. Thus, a number of investigations (Bordet and Delange, Stuber and Heim) have disclosed the influence of these substances on the coagulation of the blood. Noguchi has demonstrated the bactericidal effect of sodium oleate on tubercle bacilli. The work of Jobling and Petersen, who have studied the purely biological properties of the soaps of unsaturated fatty acids, is of particular interest: the authors have shown *in vitro* the inhibitory effect of even 0.08 per cent of these soaps on the hydrolysis of casein by trypsin. From this fact they conclude that the antitryptic power of the blood serum depends on the quantity of soaps of unsaturated acids contained in it. Further evidence in favor of this opinion is given by them in their most interesting study of caseated tissues. It appears that the elimination of lipoids from such foci by means of ether leads to their rapid hydrolysis by trypsin, and that the ether-extract exercises antitryptic properties. By treating the caseated foci with iodine, that is, by chemically saturating the unsaturated acids, autolysis is produced

in them. This circumstance has led the authors to suggest the use of iodine in the therapy of tuberculosis. Further on I shall discuss whether such a method can be considered to be correct.

In accordance with the findings mentioned above, my attention, when studying the action of *Oleum jecoris*, was naturally directed to its unsaturated fatty acids. In my experiments, I have used the sodium salts of saturated and unsaturated fatty acids, prepared by the method of Varrentrapp, as most resembling the physiological compounds in the form in which *Oleum jecoris* is absorbed in the digestive tract. Owing to the great complexity of biochemical processes in the tuberculous organism, the biological value of the substances mentioned was tested on normal guinea pigs, while taking into account the reactions of the body which are at present regarded as protective in tuberculosis. Therefore, the reaction of the organism to the introduction of soaps was estimated by determining the lipase content, the bactericidal power, the antitryptic value, the leucocyte formula, and the variations of body-weight. The soaps were injected subcutaneously, 0.02 mgm. to each gram of body-weight, in the form of a 3 per cent solution.

VARIATIONS OF LIPASE

Lipase was determined by the method of Henriot: namely, titration with a 1/100 normal solution of alkali. Two or three weeks before the experiment the normal lipase values of the guinea pigs were determined, and found to be from 18 to 19.5. After the injection of the soaps, the lipase value was tested every 2, 4, 12 and 24 hours. The results being remarkably constant, no table of results is necessary to demonstrate them; the injection of soap leads, not to an increase, but rather to a slight decrease of the lipase value of the blood. The maximum fall was recorded 24 hours after the injection, when the lipase value declined to 16 to 17; 2 and 4 hours after the injection the decrease was manifested even less. Consequently, if the increase of lipase is to be regarded as a favorable sign in tuberculosis, *Oleum jecoris*, injected subcutaneously, is not very active, and should be introduced for therapeutic purposes *per os*. In the latter case, some workers record an increase of the lipase value in the blood serum; this may probably be connected with the process of digestion (Rona). This is further confirmed by the fact that the introduction of oil *per rectum* also does not lead to an increase of the sero-lipase.

VARIATIONS OF THE ANTITRYPTIC VALUE

The antitryptic value of the serum has of late become the subject of investigation in different pathological processes. Thus, in cases of cancer, tuberculosis and typhoid fever, a high antitryptic value of the serum is assumed to be an unfavorable sign, denoting an increased destruction of tissues. In my work, the antitryptic value was tested together with the lipase value, by the Gross-Fuld method. This method has the defect of leaving a wide field for personal subjective estimation of results. However, if a constant standard be prepared, the results may be made more comparable. The investigation showed that the injection of soaps increases slightly the antitryptic value.

VARIATIONS OF THE LEUCOCYTIC FORMULA

Before undertaking the experiments, an attempt was made to determine the average leucocytic formula of normal guinea pigs. This, however, proved to be impossible, owing to considerable individual variations. This observation is confirmed in the literature (Kurloff, Howard, Löwit). Therefore, I have studied the variations of the leucocytic formula separately for each guinea pig, taking into account only the character of these variations. The following results have been gained: 3 hours after the injection of small doses (see above) of unsaturated soaps, a leucocytosis set in, which lasted six days. The injection of triple doses led, three hours after the injection, to an inconsiderable leucopenia, which changed, after 24 hours, to a leucocytosis lasting three days. In all cases, the maximal leucocytosis (number of leucocytes nearly double) took place nearly 24 hours after the injection. The morphological changes, three hours after the injection, consisted in an increase of the number of polymorphonuclear leucocytes; but after 24 hours a considerable lymphocytosis set in, which lasted usually about six days. An increase of eosinophiles was noted on the third day and later.

The general effect of subcutaneous injections of the soaps of *Oleum jecoris* was determined by measuring the weight of the animals. Guinea pigs, subjected to injections of soaps during 3 to 4 weeks, with intervals of three days between injections, did not grow thin; on the contrary, a considerable increase in weight was recorded. The soaps produced obviously no toxic effect and the metabolism did not suffer.

It was impossible, within the limits of the present work, to investigate

whether the bactericidal properties of the blood are increased by the injection of soaps; but the action of saturated and unsaturated soaps of *Oleum jecoris* on tubercle bacilli has been studied by me *in vitro*. I first investigated the effect produced by these soaps on the growth of tubercle bacilli on potato media, to which the soaps were added in different concentrations of from 0.25 to 4 per cent. After three weeks it was found that unsaturated soaps, even in a concentration of 0.25 per cent, inhibit the growth of the bacilli, while the saturated soaps give the same effect only in concentrations exceeding 4 per cent. When an emulsion of tubercle bacilli in a one or two per cent solution of unsaturated soaps is used, the effect is still greater. After 48 hours in the incubator, the preparations stained by the Ziehl method have an interesting appearance: the tubercle bacilli are pale pink, and contain dark granules, as though they were stained with methylene blue. Further, a considerable number of the bacilli have lost their acid-fastness and are stained blue. In this respect my results are similar to those of Palma. But Palma's effect was more definite and was obtained with very low concentrations of lipoids. This was probably owing to particularly highly unsaturated lipoids, the more so as their Hübli value was very high, namely, 224. It must be supposed that this dissolving of the bacilli is accompanied by changes of their antigenic power, namely, by its increase (McJunkin).

Summing up the results of this research, it may be said that the therapeutic effect of such oils as *Oleum chaulmoograe* and *Oleum jecoris* is due, not to an increase of lipase, but to a change in the chemical composition of the tissues and pathological foci. These oils help the accumulation (or formation) of unsaturated lipoids, and thereby conditions are obtained, in which, as in Palma's experiments, the unsaturated lipoids of the lymph nodes can act bacteriolytically even in a concentration of 0.001 per cent.

Now it is necessary to be extremely careful in drawing conclusions as to the significance of the increase of the antitryptic value of the blood serum brought about by the injection of the soaps of *Oleum jecoris*. As already mentioned, the increase of antitrypsin is usually regarded as an unfavorable symptom, and some authors, Jobling among them, have recommended iodine therapy to lower the antitryptic value by saturating the unsaturated lipoids in the tuberculous foci. However, although these authors understand the nature of the process correctly, their reasoning would seem to be erroneous. Owing to the funda-

mental and practical importance of this problem I shall endeavor to analyze the nature of the processes taking place in the tuberculous focus. As a result of cell destruction in such foci, proteolytic enzymes appear, which destroy the proteins and produce fever, etc. The body responds by elaborating substances which inhibit autolysis of the tissue, and the antitryptic value consequently rises. But this increase of the antitryptic value, as seen from the foregoing, shows only that great cell destruction is taking place, and it would be a mistake to suppose this to be an unfavorable sign. Therefore, a further increase of antitrypsin and an inhibition of cell destruction, brought about by the artificial introduction of lipoids, can hardly be noxious for the patient. The question is only as to the degree and the cases in which this can be done. Leaving this question aside for the time being, we must consider the problem of the healing rôle of the unsaturated lipoid from another point of view; namely, the soaps of fatty acids are obviously the form in which the fatty acids perform their biological task as such. Thus Zeuner, basing his idea on the data of numerous authors, suggests that a certain quantity of soaps is present in all the body fluids in a state similar to that in which they would be in physiological saline solution. The action of soaps upon tubercle bacilli is either bacteriolytic, or consists in creating for the bacilli an unfavorable medium. The soaps also (as has been shown above) bring about a lasting leucocytosis, which also forwards phagocytosis and bacteriolysis.

In short, this mechanism of the action of the unsaturated soaps permits us to assume a definite fundamental position as to the therapeutic use of *Oleum jecoris*. Inasmuch as a constant and lasting saturation of the tissues of the diseased organism with unsaturated lipoids is advantageous, the use of *Oleum jecoris per os* must naturally be effected in large doses, 100 to 300 gr. *per diem*. On the other hand, it is an extremely enticing idea to administer unsaturated soaps parenterically, this method permitting the introduction of these valuable substances in a concentrated form and the avoidance of harm to the sensitive digestive tract of the tuberculosis patient. Attempts are being made in this direction (Rogers, Ostromislenski, Tewkesbury, etc.). But a great number of additional experiments is necessary before a reliable mode of action is worked out.

CONCLUSIONS

The conclusions that are permissible seem to be:

1. The therapeutic action of *Oleum jecoris* may be due to the unsaturated fatty acids contained in it.

2. The subcutaneous injection of soaps of the unsaturated fatty-acid series does not lead to an increase of sero-lipase; the antitryptic properties of the blood are increased.

3. The leucocytosis brought about by the injection of soaps is permanent; an accompanying lymphocytosis has been recorded.

4. The soaps of unsaturated fatty acids act bacteriolytically and bacteriocidally upon the tubercle bacilli.

5. *Oleum jecoris* therapy must be effected in massive doses; in cases of parenteric introduction, it is necessary to base the therapy upon the ensuing biological reactions.

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PULMONARY NEOPLASMS

A Discussion of Their Increasing Prevalence, Diagnosis and Treatment[1]

CHARLES E. ATKINSON[2]

Tumors of the lung, even if we include all varieties, constitute only a small percentage of pulmonary diseases. Nevertheless, they occur sufficiently often, and are so often misdiagnosed, most frequently as tuberculosis, that a discussion of the subject seems timely. In the past, lung cancer, of the primary type in particular, has been regarded as a rarity; but medical literature has of late years noted a marked increase in its incidence, and one of our foremost journals (1) has recently emphasized the fact that pulmonary cancers to-day constitute from 3 to 5 per cent of all cancers, and that many authorities now consider lung cancer not a rare but a common form of neoplasm.

Greater diagnostic acumen and the more general use of the X-ray together share the credit of bringing to light many cases of malignant tumor that formerly would have been passed over, yet much of an apparent increase is undoubtedly actual. Many series of necropsy records, covering long periods of time, show a trebling and even a quadrupling of lung-cancer figures of late years. By way of illustration, Moise (2) cites 5 cases of primary lung cancer occurring in a consecutive series of 375 postmortems, among which were 29 cases of carcinoma. Lung cancer was the cause of death in 1.38 per cent of this series, and constituted 17 per cent of all carcinomas found. The increase of lung cancer is entirely disproportionate to any alteration of the general cancer incidence. The cause of this greater prevalence of lung cancer is not yet established, but very suggestive evidence has been adduced that the increase is a result of chronic lung irritation occasioned by the influenza epidemic.

[1] Read before the Section on Tuberculosis of the Los Angeles County Medical Society, Los Angeles, California, May 25, 1926. In the original article four cases were described in detail, but to save space the cases are here reported merely by means of legends accompanying the illustrations.

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If, in addition to carcinoma, other forms of lung new growths, such as sarcoma, lymphosarcoma, endothelioma and Hodgkin's disease, are taken into consideration, we find that neoplasms of the lung occupy a place of no negligible magnitude among pulmonary affections.

DIAGNOSIS

The symptoms of lung tumor are almost identical with those of tuberculosis, but the age of the patient affords some help in diagnosis. Tuberculosis may occur at any age, and a relatively mild type of tuberculosis after 40 is not rare; but the fifteenth to the thirty-fifth year is the preponderant age for tuberculosis, while the largest number of cancers develop between the fortieth and seventieth years. This rule is by no means absolute, for carcinoma has shown an increasing tendency during recent years to appear in early adult life, and other forms of new growth occur in the earlier years of life even more frequently. Nevertheless, if symptoms simulating pulmonary tuberculosis first appear after middle age, the possibility of pulmonary cancer should come to mind, and care should be taken to avoid error.

Among special symptoms, pain is often, although by no means always, prominent. It is sometimes sharp and stabbing in type, tends to occur early, to persist or recur frequently, and is often progressive. In some cases the seat of pain seems deep in the chest, and a distinguishing feature is that it is often worse at night. Pain, which persists after effusion develops, is especially suggestive. In certain instances pain is referred to the epigastrium, and in others, especially when the new growth has its origin in the pulmonary apex, it is referred to the shoulder and arm.

Pancoast (3) reports 4 cases of apical tumors, in which symptoms of neuritis in the shoulder and arm, together with sympathetic phenomena, including eye symptoms, were so pronounced that a cord or meningeal lesion was closely imitated. In one of this author's cases, laminectomy was performed, and it was only by a later and more thorough X-ray study that the actual seat of the tumor was found in the lung. In another of his cases, a cervical rib was suspected. In my experience a mild neuritis of the upper extremity is a fairly frequent accompaniment of pulmonary tuberculosis; therefore, I do not feel that symptoms of this nature are of very great import. Yet, if the neuritis is severe, and particularly if eye signs, such as contracted pupil, narrowed palpebral fissure and ptosis are present, care should be taken to exclude neoplasm.

Not rarely the recurrent laryngeal nerve is involved, and throat symptoms, such as hoarseness, voice weakness or complete aphonia, and, in some cases, inspiratory stridor, are noted. Such symptoms are of course not rare in uncomplicated tuberculosis, even in the complete absence of laryngeal involvement; hence, they are not ordinarily to be given great value; but, especially if severe, they do call for a painstaking investigation.

A very striking symptom in many cases is dyspnea,—a dyspnea which may attract attention at once, and which at first seems rather uncalled for or without sufficient cause. These patients many times are surprisingly well nourished, better nourished than the general run of tuberculosis patients, and the dyspnea has a tendency to be out of proportion to the general aspect of the case and loss of weight.

Cyanosis may be a marked feature, and if present it should lead to a careful investigation. Pressure on the superior vena cava may cause distention of the cervical veins and produce symptoms of cerebral congestion, such as dizziness, headache or nose-bleed. Dysphagia is not uncommon. If the location of the growth is such as to produce early obstructive symptoms, the making of an accurate diagnosis is rendered more probable.

Pleural effusion of a more or less bloody character has been considered a valuable diagnostic point. Effusions of this nature sometimes occur in tuberculosis; but, if considered together with other suspicious signs, a sanguineous effusion will sometimes help in arriving at a conclusion. Blankenhorn (4) states that if a fluid becomes bloody after repeated tappings, and if tapping produces only a temporary abatement of symptoms, this is especially suggestive of cancer. In tuberculous effusions he claims that the fluid is more often bloody at the first tapping and clear at subsequent ones, and that tapping usually gives relief from symptoms.

Cough is usually present, but it may be absent. It may be either dry or productive. The sputum may be mucoid or mucopurulent. Blood-stained sputum is not infrequent, and frank hemorrhages may occur. Sputum of the prune-juice type, or sputum containing the so called currant-jelly masses, is regarded by some as of special significance. Rarely, particles of the tumor may be expectorated, and Hampeln has called attention to the presence in the sputum of certain unpigmented, polymorphous cells, which he believes to be pathognomonic. Tubercle bacilli are, of course, absent unless the patient also has tuberculosis.

Many of the older pathologists held that cancer and tuberculosis were antagonistic. To-day some authorities have the feeling that, far from

an antagonism, tuberculosis may actually provide the local irritation which gives rise to cancer. Letulle (5) reports two instances of primary cancer developing in the vicinity of tuberculosis in active evolution, and Gibson and Findlay (6) report a case of primary lung cancer following tuberculosis. One of my own cases showed a similar sequence of events. Recent studies, especially those of Broders, indicate that tuberculosis is fairly frequently associated with pulmonary neoplasm. In fact, Broders (7) states that "the reason pathologists are not finding tuberculosis more frequently . . . . is that the pathologists are satisfied to find the malignant neoplastic condition, and therefore fail to make a thorough search for tuberculosis." In this connection the point to remember is that tuberculosis and cancer may occur together, and not to rule out either just because the other condition is present.

Among general symptoms, fever may or may not be noted. Night-sweats occur in some cases. Fishberg states that in nearly all cases, regardless of temperature, the pulse is of normal rate, and he regards this as a valuable diagnostic point. In regard to cachexia, most authorities state that this develops more slowly and is less pronounced in lung cancer than in other forms of malignant disease, and this agrees with my observations.

Physical Examination: In the early stage the physical signs are often entirely negative. Even at a later stage signs are usually scanty and indefinite, but this very indefiniteness may cause suspicion. One point worthy of emphasis is that signs of venous obstruction are sometimes manifest to the eye, and the cervical veins may be dilated or the superficial veins of the chest may be prominent. Evidence of this nature, of marked degree, is uncommon in tuberculosis and should excite suspicion. Percussion over a neoplasm of moderate size often elicits a flat note, which is rare in uncomplicated tuberculosis, and, if the growth occupies the middle lung zone, resonance is often present both above and below the flat area. If the abnormal signs are found in the middle or lower part of the lung this militates against tuberculosis, but may cause confusion with pleural effusion or abscess. Weakened or absent breath-sounds over the tumor are fairly common. Râles may or may not be detected; but, if absent, the combination of a flat percussion note with weak or absent breath-sounds and without associated râles, is highly suggestive. As the tumor mass enlarges, the heart and trachea are often pushed to the opposite side of the chest, while in tuberculosis scar-shrinkage results in drawing the mediastinal organs toward the affected side.

Special Methods of Examination: A certain proportion of lung tumors have their origin in the bronchi, and bronchoscopic examination has been of material aid in making a diagnosis of new growths in this location. The use of the endoscope, as practised by Jacobaeus, may also yield valuable data if the growth has its origin in or encroaches on the pleura, but both of these methods are of advantage only to those of wide experience in their use.

Roentgenological examination is extremely valuable, but is not an infallible guide. The shadows are not always distinctive, and this is particularly true as regards early apical tumors, which may show merely as a localized haziness. A new growth is usually manifest as a more or less dense, roughly circular shadow, which may be circumscribed, or may shade off gradually. It may be accompanied by smaller metastatic shadows. The shadow or shadows may originate in the lung parenchyma or at the hilum. In the latter case, processes sometimes radiate into the lung. The shadows cast by multiple tumors are usually larger than tuberculosis shadows, and the surrounding lung is fairly clear. Secondary carcinosis may simulate miliary tuberculosis, but the carcinoma shadows are likely to be most thickly set in the lower part of the lung. Wholly negative cancer reports have been given from X-ray study, but, as Thomas and Farmer (8) state, it is rare to have negative roentgen-ray findings in any case so far advanced as to present symptoms. In my own experience there has usually been something at least strongly suggestive in the X-ray picture of neoplasm; and, not uncommonly, merely a glance at the screen suffices to clear up a doubtful diagnosis.

If effusion is present, this should be aspirated and an X-ray examination made immediately. A diagnostic pneumothorax may also prove helpful in cases of doubt.

Differential Diagnosis: As previously stated, chest tumors are usually diagnosed as tuberculosis, yet if the case is carefully studied by the X-ray, the more or less rounded and homogeneous neoplastic shadow is not apt to be mistaken for tuberculosis mottling. An intrathoracic thyroid or an enlarged thymus may lead to error, and, even more rarely, actinomycosis, nocardiosis or hydatid disease may cause difficulty. In doubtful cases the possibility of the presence of encysted empyema or lung abscess, or of a cold abscess from Pott's disease, should be recalled to mind. An abscess shadow is ordinarily of uniform density, but often has a hazy, irregular border shading gradually into the surrounding tissues, and in some cases the centre is rarefied and contains a fluid level. An unre-

solved or caseous pneumonia is also a possibility to be considered. A new growth may be diagnosed as aneurysm, or the reverse may occur. Fluoroscopic study will nearly always reveal aneurysmic pulsation, but arterial movements transmitted through a new growth may simulate pulsation very closely. Syphilitic gumma or indurative processes may require differentiation. Thoroughness in conducting the examination and, if necessary, repeated examinations, will as a rule prevent mistakes. In doubtful cases of mediastinal shadow, the esophagus should be filled with barium for fluoroscopic study.

Once a new growth is diagnosed, the fact should be recalled that benign tumors of the lung are very rare; therefore, the neoplasms which require differentiation are chiefly carcinoma, sarcoma, lymphosarcoma and endothelioma, and the tumor-like masses of Hodgkin's disease. The granulomata of Hodgkin's disease are usually shown as a dense shadow or coalescing shadows, extending beyond the mediastinum, with a border which may be either irregular or clearly defined. The shadow is occasionally only unilateral, and thus may be confused with primary cancer, which is also unilateral as a rule. It may be difficult or impossible to distinguish the shadows of lymphosarcoma and Hodgkin's disease, but here the history and clinical course are helpful.

TREATMENT

Surgery still holds the place of first importance in the treatment of neoplasms of many parts of the body, but pulmonary neoplasms are not readily amenable to this form of treatment. Excision of the lung has a high mortality, but a few cases of successful removal of malignant tumors by operation have been reported. If the new growth is small and centrally located between the hilum and pleura the chances for success are increased.

The Roentgen-Ray and Radium: The literature now contains a considerable number of reports of the treatment of lung neoplasms by means of the X-ray. In lymphosarcoma and Hodgkin's disease, in particular, life has been prolonged for years, and in a number of cases apparent cure has resulted. Most of these cases were treated before the days of the employment of high voltage and short wave-lengths in deep therapy, so that even better results are to be looked for in the future. The X-ray has been employed in a fair number of cases of lung cancer, with many unfavorable, but with a few favorable results. For example, Schroeder

(9) reports a case of malignant tumor of the lung, in which prompt recovery followed two applications of intensive, deep roentgen therapy. Films made before treatment revealed a massive growth, while afterward the X-ray showed complete disappearance of the tumor and the patient was restored to active work.

Yonkauer (10) reports a case of lung tumor, originating in the bronchial passages, apparently malignant, which was successfully treated by the simultaneous use of radium capsules, introduced through the bronchoscope, and the external application of radium.

Among other remedies for cancer in general, preparations of selenium and copper have been used abroad for a number of years, with some success. A mode of treatment of great promise is the intravenous use of lead, a method originated by W. Blair Bell. In fact, Bell's results were so clear-cut as to lead Carter Wood (11), who made a personal investigation of the method, to state that it "represents the most important advance in the treatment of inoperable cancer since the introduction of

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FIG. 1. (Case 1.) Female, aged 30. Nutrition well retained, but hemoglobin only 50. Chief symptom, cough. Note rounded homogeneous shadow extending from the hilum nearly to pleura. Pronounced flatness (practically no râles) over this area. No evidence of neoplasm elsewhere. *Diagnosis:* Primary sarcoma of lung.

FIG. 2. (Case 2.) Female, aged 50. Tuberculosis of slight extent but of long standing, in right apex, and two small ulcers on vocal cords. Weight-loss, 15 pounds within two months. Note rounded shadow in third right interspace. Physical signs practically negative. On first consultation (November 28, 1924) patient was thin but well nourished, and seemed almost well, but obstructive symptoms and effusion developed later. Death occurred June 15, 1925. *Diagnosis:* Primary lung carcinoma confirmed by necropsy.

FIG. 3. (Case 3.) Female, aged 22. First seen February 28, 1924. Usual symptoms suggestive of tuberculosis, plus diarrhea. Very weak, extreme emaciation, and in apparently hopeless condition. Physical signs almost negative except for dulness over right upper lobe, and generally weak breathing on this side. Skin extremely dry and scaly. Oval shadow in right lung, which on screen study was found to be centrally located.

FIG. 4. (Case 3.) Thyroid was administered in doses from 1 to 6 gr., followed by remarkable improvement. This film (made three months after fig. 3) shows entire disappearance of shadow. Later symptoms suggestive of Vincent's infection (Wassermann negative) developed, and despite the use of iodides, arsphenamine and other ordinarily effective remedies, death occurred August 18, 1925. No autopsy was obtained and exact diagnosis is in doubt.

FIG. 5. (Case 4.) Male, aged 59. First seen July 17, 1923. History of pulmonary tuberculosis for many years and of an old luetic infection (Wassermann ++++). Under antituberculosis regimen plus treatment for syphilis, patient improved greatly, and in the summer of 1925 he was practically well. A few months later he failed rapidly, and roentgen study on October 26 showed a rounded, nonpulsatile shadow extending to the right in the fourth to the sixth interspace. Death occurred within a few weeks. No autopsy was obtainable, but the case appeared to be one of primary lung carcinoma.

FIG. 1

FIG. 2

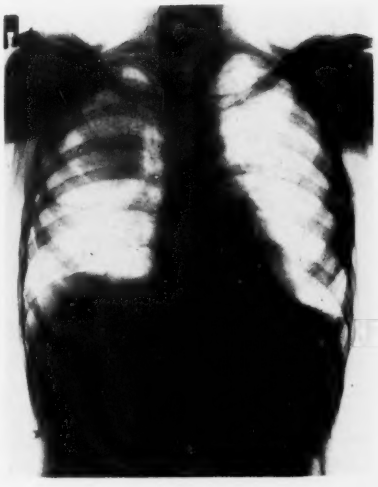

FIG. 3

FIG. 4

FIG. 5

X-ray and radium." The lead solution is not obtainable for general use at present.

In this country Ochsner (12) has recently advocated the use of colloidal gold for inoperable and secondary cancers. This remedy is simple to use, and may be administered either by mouth or intravenously; and, if we are intent on doing our utmost for these unfortunate individuals, this form of therapy merits a thorough trial. For tumors of the sarcoma type, Coley's fluid should not be forgotten. Although the combined erysipelas and prodigiosis toxins is a remedy conceived primarily for osteosarcoma, I have seen good results from its use in sarcoma in other parts of the body.

Endocrine therapy, especially thyroid therapy, has been forcefully advocated by Robert Bell, Page and Bishop, Sajous (13), and other recent writers. Bell's report covered several recoveries of over nine years' standing; and, as we are glad to offer any ray of hope to this class of patients, thyroid therapy should not be disregarded. Iodides may be used alone or in conjunction with thyroid to facilitate its effect. Potassium salts, strongly advocated by Ross (14), constitute another mode of attack. As much as 90 to 180 grains a day of potassium acetate, citrate or phosphate may be given and continued for months at a time. Ross was a thorough student, and related remarkable results in advanced inoperable cancer, and this line of treatment should not be lightly passed over.

The dietary should be given careful attention. Regardless of our theories as to the origin of cancer, many are now coming round to the view that some general factor influences the bodily economy and paves the way for the development of cancer, and Hoffman, Kellogg and Bulkley (15) have shown that cancer is extremely rare among peoples living on a meatless dietary. Bulkley and others strongly emphasize that the exclusion of meat from the menus of cancer patients is productive of much good. Aside from a vegetarian diet, condiments, tea, coffee, cocoa and tobacco should be barred, and, in general, only a moderate quantity of food should be eaten. The necessary measures to prevent intestinal stasis and autointoxication are also very important. A limited experience leads me to believe that these simple measures have value.

COMMENT

In cases 1 and 2 (see illustrations) the advisability of roentgen treatment was discussed; but, as I did not then place a high valuation on this form of therapy for lung neoplasms, its use was not strongly urged. In view of what I have since learned, if a case of malignant tumor of the lung again presents itself I shall forcefully urge that roentgen therapy be used.

CONCLUSIONS

Primary malignant tumor of the lung has increased decidedly in recent years, and this increase is out of all proportion to the general increase in cancer incidence. Heretofore, lung neoplasms have not offered a fertile field for treatment because only secondary tumor deposits have ordinarily been recognized, and when primary neoplasm has been diagnosed the growth has usually been so far advanced as to offer little chance for successful attack. Lung tumors are most frequently diagnosed as tuberculosis. Since pulmonary malignant tumor is now known to be definitely on the increase, special efforts should be put forth to detect the condition at an early stage.

Of special diagnostic measures, the X-ray is the most important, but thoroughness in securing the history and in conducting the examination are essential.

For therapy, the X-ray is again the agency of greatest value, but other methods are of undoubted value, and all methods should be given consideration. The outlook is no longer hopeless; and, with efforts concentrated on the problem, it seems fairly probable that in forthcoming years a not inconsiderable number of these patients will be saved.

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SPONTANEOUS PNEUMOTHORAX IN PULMONARY TUBERCULOSIS

A Brief Statistical Summary and Discussion of Cases Occurring at the Fitzsimons General Hospital, Denver[1,2]

J. A. WILSON[3]

In this report I have not included the cases of spontaneous pneumothorax occurring during treatment by induced pneumothorax, except in one instance in which a spontaneous pneumothorax occurred on the side opposite to that in which the induced pneumothorax was being maintained. Cases have also been excluded in which the pneumothorax occurred at once, or shortly after a successful or unsuccessful attempt to withdraw fluid from the pleural cavity had been made, since it was believed that these pneumothoraces were probably due to an accidental needle puncture of the lung or to the tearing of an adhesion from the too rapid or too extreme expansion of a partly collapsed and adherent lung.

INCIDENCE

The Fitzsimons General Hospital began to function in the autumn of 1918. On December 31 of that year there were 609 patients in the hospital. On the last day of each succeeding year there were, in order, 913, 742, 977, 1,169, 1,170, 1,353, and 1,055 patients. During the first few years approximately 90 per cent were tuberculosis patients, the great majority with pulmonary involvement. Later the proportion of non-tuberculous cases increased, so that in 1922 approximately 20 per cent belonged to this class, and in 1925 this had increased to 30 per cent.

From the opening of this hospital until June 1, 1925, I have found records of 96 simple spontaneous pneumothoraces, one spontaneous pneumothorax complicating an induced pneumothorax on the opposite side, 2 cases in which spontaneous pneumothorax occurred on each side,

[1] Read in part before the Denver Sanatorium Association, Denver, Colorado, January 26, 1926.

[2] Published with permission of the Surgeon-General, U. S. Army, who is not responsible for any opinion expressed or conclusions reached herein.

[3] Major, Medical Corps, U. S. Army.

and 3 cases in which two pneumothoraces occurred on the same side. All of these cases are of the old-fashioned clinically frank variety of pneumothorax, none of them being of the "pleural ring" or "local pneumothorax" type.

This may seem like a small series for a hospital of this size. However, in view of the exceptionally free use of the X-ray, of the frequent visits of consultants to all wards, of the high percentage of autopsies (50 per cent), and of the use of postmortem plates in some cases in which autopsies could not be done, it is believed that only a very few cases could possibly have gone unrecognized, and that these figures represent the true proportion of pneumothoraces occurring.

Figures obtained from different sources as to the frequency with which this complication occurs in pulmonary tuberculosis show a marked variation. The extremes that I have found are those of Barth (1), who believes it occurs in only 0.2 per cent of cases, and those of Kahn (2), who believes it occurs in 10 to 15 per cent of all cases. These marked discrepancies can be only partly explained by presuming that different classes of phthisical patients were observed. Other discrepancies are due to some observers basing their figures on clinical material, and others basing theirs on postmortem material. Thoroughness of clinical observation, and especially free use of the X-ray, will disclose cases ordinarily missed. Consequently, figures compiled from earlier sources, when the X-ray was used rarely or not at all, will not, perhaps, be of the same value as more recent figures.

From autopsy records, Lord (3) believes that pneumothorax is present in about 10 per cent of fatal cases; Williams (4) gives 10 per cent; Weil (5), 10.1 per cent; and Powell and Hartley (6), 8.2 per cent. From clinical material, Drasche (7) found it present in 1.46 per cent of 26,231 cases; Morris (8), in 449 active cases and 187 inactive cases, found it present in 2.64 per cent; Blumberg (9), in 425 cases, found it present in 3.1 per cent; and Fishberg (10), at the Montefiore Home, found it present in 3 per cent of cases. Fishberg believes that, of all cases, one out of every twenty (5 per cent) will develop the complication. West and Lebert (11) are in accord with this figure; Gray (12) believes it more frequent and Chambers (13) and Drasche (13) less frequent. Sergent and Courcoux (14) believe that only one or two per cent of tuberculosis cases develop pneumothorax. Gaillard (15), in 1896, obtained reports from all institutions in France handling tuberculosis patients, as of a fixed hour and day, and found pneumothorax present in 1.054 per cent of cases.

It is obvious that an institution like the Brompton Hospital, whose cases are mostly terminal ones, might have a much different percentage of pneumothorax cases than a sanatorium receiving only incipient cases. Kahn (16), in 300 consecutive cases of *phthisis pulmonalis* in his own practice, saw 33 cases of pneumothorax, not all verified by X-ray. His high percentage can be explained only by coincidence, or by his interest in the treatment of this class of patients having drawn an undue proportion to him. Gaillard's figures (15), noted above, are based on a great many cases, and are probably as reliable as any, yet they are open to serious criticism. First, those in hospitals and sanatoria are not necessarily truly representative of all tuberculosis patients. Second, the X-ray was not at that time (1896) used to establish diagnosis in cases unrecognizable otherwise. Third, by just as many times as the length of life of cases of pulmonary tuberculosis without spontaneous pneumothorax exceeds the length of life of cases of pulmonary tuberculosis with it, so will a cross-section of their lives at any one period show that many times a falsely low number of spontaneous-pneumothorax cases.

Unfortunately, the statistical material at the Fitzsimons General Hospital is, as yet, not well enough worked up to permit it to be of definite value as to this point. However, it is obvious that our figures will approach the lowest percentages quoted. It is to be hoped that the Veterans' Bureau, which has had an unprecedented opportunity to follow, from development to death, so large a number of cases closely, will soon furnish us more valuable statistics than any previously collected.

IMMEDIATE CAUSES OF SPONTANEOUS PNEUMOTHORAX

Data, available in our records, are insufficient to furnish much of value on this point. However, the great majority of our cases were bed-patients at the time of onset, and most of them must have been in bed when the complication occurred. The astonishing point is brought out that in only 4 of the 102 cases was the pneumothorax mentioned as developing with or immediately after a cough.

Gray (12) believes that the tearing of the visceral pleura is usually caused by a cough or some unusual effort. Lord (17) does not think that effort plays much of an etiological part, inasmuch as in 25 cases seen at the Massachusetts General Hospital, 14 occurred in patients while in bed or sitting up. Sergent and Courcoux (18) state that anything that brings about increased intrapulmonary pressure, such as coughing,

muscular effort, etc., will act as an immediate cause of the pneumothorax, and this opinion is apparently generally held by phthisiologists.

An etiological relation of cough to spontaneous pneumothorax is apparently not confirmed by our records. In this connection, it should also be remembered that cough, occurring at the beginning of spontaneous pneumothorax, may be due to the pleural irritation immediately resulting from injury to the pleura. Nor does any interpretation of pulmonary mechanics lend itself to the theory that any part of the act of coughing, or of an increased pulmonary pressure incident to strain or coughing bears any such relationship. The first part of the act of coughing entails a *partial* expansion, with *all* chest muscles and the abdominal muscles *under tension*. It is not a *full* and *free* expansion. During this part of the act, intrapulmonary pressure is lowered. The second part of the act is brought about by a closure of the glottis, a fixation, or even contraction, of the chest, and a further increase in the tension of the abdominal muscles that force the diaphragm up and *increases* the intrapulmonary pressure, but *decreases* the volume of the lung. In the lung itself this increase of pressure is transmitted to all parts of the lung equally. Through an open bronchus it may be carried to a subpleural cavity, but it is transmitted, as well, to the alveoli immediately surrounding the cavity. Around the cavity the pressure in the tissue is just as great as it is within the cavity. Distally, where the two pleural surfaces are in contact, the pressure must be equal to, or greater than, that within the cavity, as the chest is held fixed or actually decreases its circumference. The lung cavity must actually *decrease* in size during this part of the act of coughing. During the third part of the act the glottis is opened, air rushes out, intrapulmonary pressure is *lowered*, the lungs further *decrease* in size, and pulmonary cavities also *decrease* in size. It is evident that no part of this act, or any part of an act increasing the pulmonary pressure, that is, decreasing the lung volume, can account for a tear in the visceral pleura.

Another phase in the mechanism of respiration that must be considered, in attempting to account for the immediate cause of pneumothorax, is the inspiratory phase. During inspiration there is a decrease in intrapulmonary pressure, and a negative pressure is produced. This negative pressure is theoretically and actually greatest in the alveoli just beneath the visceral pleura. It tends to produce enlargement of these alveoli, as well as enlargement of a subpleural cavity. The force that promoted this expansion is ordinarily not great, as the increase in negative pressure

during even deep inspiration amounts to only a few millimetres of mercury. The amount of expansion produced by this negative pressure in a cavity is probably less than in an equally large area of healthy alveoli. Also, it is presumed that ordinarily, even in phthisis, the reserve expansibility of the remaining normal alveoli is much greater than expansive capacity of the chest, and probably a greater proportion of expansion will occur in this healthy tissue than in a more or less fibrously walled cavity. If the subpleural wall of such a cavity is thin and necrotic, if the pleura over the area is necrotic, and if there are *no adhesions*, it is possible that the increase in size of the cavity from a deep inspiration might cause the rupture of the cavity. As adhesions are usually present over an inflamed or necrotic patch of pleura, it is not believed that the simple expansion of a cavity with inspiration is a frequent cause of tears of the overlying pleura.

Still a third point to be considered in the production of spontaneous pneumothorax is the change in the relationsbip of the pleural surfaces during respiration. MacLeod (19) claims that during respiratory movement there is practically no movement of the visceral pleura over the parietal pleura in the upper anterior and upper posterior parts of the chest, or in the extreme apex; that is, the expansion (what there is of it) takes place in a direction at right angles to the pleural surface. In the lower part of the chest the condition is different. Here expansion is greatest and the negative pressure of inspiration highest. During inspiration the lower part of the chest expands and the diaphragm descends. This separates the two parietal layers of pleura in the phrenicocostal sinus, and converts this sinus into a broad, deep space into which the lung descends. This movement is most marked in the midaxillary line, where the lower margin of the lung may move up and down over a space of 9 cm. This means that the pleura over this part of the lung moves over the costal pleura from a few to 9 cm. during each respiration. This movement will be greatest at the base, and diminished above. In dry pleurisy, it is in the lower lateral aspect of the chest that a friction rub is most prominent, for it is here that the movement of one pleural surface over another is most marked.

When, in tuberculosis, adhesions begin to form over the upper part of the lung, these can go on uninterruptedly to a complete closure of this part of the pleural cavity, inasmuch as there is no movement between the pleural surfaces. However, when adhesions begin to form over the midportion of the lung, they are constantly under strain because of the sliding

movement of the pleural surfaces, and it is logical to presume that this lateral stress, brought to bear on a new adhesion over a necrotic area or new-formed cavity, is the most frequent cause of spontaneous pneumothorax. This lateral stress will be most marked during a *full, free* inspiration, such as occurs in sighing or the deep, sighing inspirations of sleep; and it is believed that it is respiratory acts of this character, rather than coughing, sneezing or straining, that are responsible for the pleural ruptures of pneumothorax.

SYMPTOMS AND DIAGNOSIS

One of our cases developed with a sharp chill, no other symptoms appearing for many hours. In another the onset took place with a sudden rise in temperature, unaccompanied by other symptoms and signs, and only hours later did frank symptoms of pneumothorax appear. In still another case, one with fibrocavernous phthisis complicated with asthma, the patient died in what was apparently a typical asthmatic attack. After death it was found that he had a large pneumothorax. In 21 of the 102 cases, the pneumothorax was occult. In some of these concealed cases no change of symptoms of any kind was noted, and the pneumothorax was discovered on routine chest or X-ray examination. In other cases there was so gradual an increase in symptoms, or so insidious a development of new symptoms, as to arouse no thought of pneumothorax, and the complication was discovered only when the persistence of the symptoms led to a thorough examination of the chest. In 6 of these occult cases the diagnosis was made only at autopsy or from a post-mortem X-ray plate.

A study of our cases brings out nothing new in diagnosis. It does, however, emphasize the point that any new symptom or an increase of existing symptoms, not obviously accounted for otherwise, should lead to a careful reëxamination and new chest-plate. These measures will almost invariably enable one to diagnose a pneumothorax. The X-ray is the most valuable single diagnostic agent. However, Dunham (20) admits having twice been unable to make a diagnosis from the X-ray plates.

DEGREE OF PULMONARY COLLAPSE

Our pneumothoraces were classified according to the degree of collapse developing within the first few days, and the presence or absence of mediastinal displacement, with the hope that thereby information of

some prognostic value could be obtained. All cases in which the affected lung was fully collapsed against the vertebral column, except for apical adhesions at or above the second rib, were considered as completely collapsed. Cases, in which the lung was held out by adhesions below the second rib, as well as those in which, in the absence of adhesions, the collapse was not complete, were considered as incompletely collapsed. The cases, in which there were no apical adhesions and a true complete collapse occurred, were so few that it was believed that the broader classification served the purpose better. The presence or absence of mediastinal displacement was in most cases determined by chest-plates,

TABLE 1

Classification as to degree of collapse

	cases
Class I. Complete collapse with mediastinal displacement	46
Class II. Complete collapse without mediastinal displacement	4
Class III. Incomplete collapse with mediastinal displacement	30
Class IV. Incomplete collapse without mediastinal displacement	18
Class V. Undetermined as to one or both of these points	9
Classes I and III. With mediastinal displacement	76
Classes II and IV. Without mediastinal displacement	22

TABLE 2

Class I. (42 cases)	37 dead	5 living
Class II. (3 cases)	3 dead	
Class III. (27 cases)	22 dead	5 living
Class IV. (16 cases)	11 dead	5 living
Class V. (8 cases)	7 dead	1 living
Classes I and III. (69 cases)	59 dead	10 living (14%)
Classes II and IV. (19 cases)	14 dead	5 living (26%)

either antemortem or postmortem, or by autopsy; in a few cases the presence or absence of a change in the position of the heart, as determined by physical examination, was the only basis on which this point was decided. In 9 of the pneumothoraces, one or both of these points could not be determined with sufficient accuracy to permit of a more specific classification.

If we consider the cases of table 1 from a viewpoint of prognosis, discarding for this purpose the one case which was under treatment with an induced pneumothorax, and the 5 cases of double spontaneous pneumothorax, we find the relation of the dead to the survivors as shown in table 2.

Among those who died, and in whom we know the date of onset of pneumothorax and date of death, we find the average length of life as in table 3.

Of those who are living and in whom the date of the pneumothorax can be determined, we find the length of life as in table 4.

As shown above, of those cases of pneumothorax in which there was mediastinal displacement 14 per cent are living, while of those in which there was no mediastinal displacement 26 per cent are living. The number of cases in the latter class is so small that deductions are risky.

TABLE 3

Class I. (30 cases)	5 months
Class II. (2 cases)	14 months
Class III. (20 cases)	5 months, 13 days
Class IV. (8 cases)	1 month, 15 days
Class V. (6 cases)	1 month, 11 days
Classes I and III. (50 cases)	5 months, 7 days
Classes II and IV. (10 cases)	4 months, 1 day
All cases	4 months, 8 days

TABLE 4

Class I. (4 cases)	3 years, 4 months, 12 days
Class II. (None)	
Class III. (5 cases)	2 years, 1 month, 9 days
Class IV. (3 cases)	1 year, 8 months
Class V. (1 case)	9 months

Nevertheless, we can perhaps say that pneumothoraces without mediastinal displacement are less fatal than when mediastinal displacement is present. With this exception no deductions of any prognostic value can be derived from an analysis of this classification of cases.

STAGE OF THE DISEASE

Fishberg (4) states that spontaneous pneumothorax is most common in hospitals for far-advanced cases of tuberculosis. He also expresses the opinion that pneumothorax would be much more frequent if it were not for the protection afforded by the pleural adhesions so characteristic of tuberculosis. He evidently believes that pneumothorax is due to the rupture of subpleural cavities or caseous tubercles over which no pleural adhesions have formed.

Sergent and Courcoux (14) believe that spontaneous pneumothorax is more likely to occur in the acute forms of tuberculosis or in its early stages. Powell and Hartley (6) consider it most common in acute pneumonic phthisis; Weil, that it occurs in the early stages; while Gray (12) states that "it may occur in early or moderately advanced cases." Apparently, the consensus of opinion is against its frequent occurrence in far-advanced caseofibrous tuberculosis, since only one of those whom I have cited expressed a contrary view.

In 99 of our cases it was possible to fix fairly accurately the date when the tuberculosis first became clinically manifest. If we accept this date

TABLE 5

	cases
During the first six months	15
During the second six months	12
During the second year	27
During the third year	19
During the fourth year	10
During the fifth year	5
During the sixth year	5
During the seventh year	2
During the tenth year	1
During the eleventh year	2
During the twelfth year	1

TABLE 6

	cases
Minimal B	1
Moderately advanced C	1
Far advanced A	7
Far advanced B	14
Far advanced C	72
Far advanced A, B, C undetermined	3

as the date of incidence, the spontaneous pneumothoraces then occurred, by year of disease, as shown in table 5.

Again, 98 of our cases could be fairly definitely classified as to stage of the tuberculosis, as appears in table 6.

A study of X-ray plates and postmortem records of the 15 cases occurring during the first six months revealed only three cases of pneumonic phthisis. The other cases were frankly of the more chronic types. Only one was a minimal case.

In the absence of statistics, showing at large the total tuberculosis cases living *by year of disease* and *by stage of disease*, and of the same statistics for the tuberculous population from which we have drawn our pneumothorax cases, a comparison of our figures with those of others would not be very conclusive. However, the Fitzsimons General Hospital differs from many other institutions in that it does not refuse to take far-advanced cases, nor are its incipient and early cases forced to leave for financial reasons, so that I believe that our tuberculosis patients more truly represent the tuberculous population throughout the country than is usually the case in sanatoria.

From a study of the accompanying tables it is apparently safe to say that the great majority of spontaneous pneumothoraces occur in far-advanced cases of the ordinary caseofibrous or fibrocaseous type, and in cases which are actively progressing. Therefore, we cannot agree with the majority of views expressed above, that this complication is more common in early cases, or in acute or pneumonic forms.

SIDE INVOLVED: PROGNOSIS

James (22), in one series of 85 cases, found 49 pneumothoraces on the left and 36 on the right; in another series of 96 cases there were 55 left and 41 right. Powell and Hartley (6) combined their cases at the Brompton Hospital with cases cited by Louis, Walsh and West, a total of 234 cases. They found 139 on the left and 95 on the right. Drasche, in 198 cases, found 55 per cent on the right. Emerson (24) cites Reynoud, Houston and Soussiers to the effect that pneumothoraces occurred twice as frequently on the left as on the right side.

The reason usually given for this greater frequency of spontaneous pneumothorax on the left is either that the left lung is more often involved than the right, or that lesions are more active in the left than in the right lung. No figures are given to support these opinions.

Weil (25) has advanced the opinion that a left-sided preponderance is due to the fact that the "most motile part of the lung is the left over the heart." This is the only remark I have seen in the literature in which the possible relationship of the heart to spontaneous pneumothorax is considered. The opinion has been several times expressed that left-sided pneumothoraces are more fatal than those on the right. It is usually stated that this is due to the more serious interference of the former with the heart's action. No figures supporting this opinion have been seen.

I have excluded from our cases the case of spontaneous pneumothorax complicating an induced pneumothorax, the second of four double pneumothoraces, and a case of double pneumothorax in which I was unable to determine on which side the first pneumothorax occurred. This leaves 99 cases; 59 of these occurred on the left and 40 on the right.

Adding up the cases cited above, by James, and Powell and Hartley, we find that, of a total of 415 cases, 243 were on the left and 172 on the right, or 59 per cent on the left and 41 per cent on the right, which is very nearly the same as our own percentages, 60 per cent on the left and 40 per cent on the right.

Of our pneumothorax cases who are dead, the average length of life of 44 left-sided cases was four months and one day; and of 29 right-sided cases, five months and six days. The difference in the average length of life is obviously not enough to justify any deductions. Of 59 left-sided cases, 47 are dead and 12 living; that is, 80 per cent dead and 20 per cent living. Of 40 right-sided cases, 33 are dead and 7 living; that is, 82 per cent dead and 18 per cent living.

From the above we are apparently justified in concluding that there is little or no difference in the mortality rates of right and left-sided spontaneous pneumothoraces.

In an effort to determine the cause for the preponderance of left-sided pneumothoraces, I obtained a disinterested check of 107 of our autopsy reports of cases of pulmonary tuberculosis. In 46 the most marked involvement was on the left; in 45 on the right; and in 16 it was impossible to tell from the record which side was most involved. I also asked Captain John DuB. Barnwell, our roentgenologist, to check over a series of routine plates, noting which side was most involved. He was not informed as to the reason for the request. Of 532 plates so checked, 255 showed the most involvement on the right and 215 on the left, while in 62 it was approximately the same on both sides.

The theory advanced that the left-sided preponderance of pneumothorax is due to greater or more frequent involvement on the left is not borne out by these figures. The theory of a more frequent, greater activity on the left is also largely nullified, as a more frequent and greater activity, sufficient to account for a 3 to 2 preponderance of left-sided cases, should show up on X-ray plates, especially at postmortem, as a greater involvement on the left.

It is not believed that Weil's theory (25), that this preponderance of left-sided pneumothoraces is due to the "most motile part of the lung

being over the heart," quite goes to the root of the matter. In the first place, the heart's action probably does not at all increase the movement between the pleural surfaces, but rather acts only by causing more rapid changes in intrapulmonary pressure, which, it is true, will be most marked just over the ventricles. However, arguments have been advanced above to prove that changes in intrapulmonary pressure can rarely of themselves produce pneumothorax. Moreover, only rarely are pleural ruptures noted in this area in cases coming to autopsy, the most frequent site being in midaxilla at about the level of the fifth rib. Also, marked involvement of this area of the lung overlying the heart is not very frequently noted at autopsy.

Perhaps another theory, based, like Weil's (25), on the effect of the heart's action, will more plausibly account for this left-sided frequency. In the normal chest the sudden systolic emptying of from 40 to 90 cc. of blood from each ventricle is compensated for by an increase in the size of the aorta and pulmonary vessels, a slight lift of the diaphragm, some shift in the position of the pericardial fluid, probably a slight shift of the mediastinum, and, lastly, by a change in intrapulmonary pressure and some shift of pulmonary tissue immediately over the heart. This sudden slight change in intrapulmonary pressure is probably, to some extent, distributed throughout the lungs, but that it is most marked near the heart is evidenced by the cardiorespiratory whiff so frequently heard along the left margin of the heart. How slight, as a whole, is this change in intrapulmonary pressure, and how little it is transmitted to the pleura through alveolar tissue, can be easily gauged when one does a left-sided artificial pneumothorax, when it will be found that the water manometer will vary with the heart's action not more than a small fraction of a centimetre.

These conditions are changed in advanced phthisis. Usually there is some fixation of the mediastinum; frequently, left-sided pleuropericardial adhesions, which will transmit the systolic tug directly to the left lung; frequently, fibrous bands running through the pulmonary tissue and transmitting this tug much more directly and with much less dispersion than does normal lung tissue; and, very frequently, there is a greatly thickened or fibrous pleura between the upper and middle lobes, and the line of this thick interlobar pleura runs directly over the active left heart on one side and over the chest-wall in the midaxillary region on the other side. It seems quite reasonable to suppose that with the lungs in full inspiration and the heart pumping out the unusual amount of blood

brought to it at inspiration, its heavy tug can be transmitted by abnormal fibrous connections to a caseous tubercle or subpleural cavity bound by adhesions to the costal pleura, and that a rupture of the pleura will occur in a sufficient number of such cases to account for the left-sided preponderance of pneumothorax.

Wiggers (26), in his book *Circulation in Health and Disease*, notes that during inspiration both borders of the heart move to the right. This would tend to augment the systolic pull on the left and is probably another factor in the mechanism of some left-sided pneumothoraces.

DEATHS AFTER SPONTANEOUS PNEUMOTHORAX

Kahn (2) states that 25 per cent of spontaneous-pneumothorax cases die on the first day and 25 per cent more during the remainder of the first week. He believes that the deaths are due to suffocation or cardiac embarrassment, and that most of the cases have an infected pleural cavity.

Lord (3), reporting Drasche's 198 cases, states that 71 per cent die during the first fourteen days. He also cites West, who, in 39 cases, had 10 die on the first day, 18 in the first week, and 60 per cent during the first month. Fishberg (27) states that 90 per cent die within a month. Capps says that pneumothorax cases rarely recover. Morse (28), in 51 cases, reports 80 per cent of deaths occurring in a year and 10 per cent living more than five years. Spengler (29) reports 10 recoveries, with arrest of the disease in 6. Powell and Hartley (30) report 58 cases, all of whom died, 1 living twelve months, 1, eight months, 1, seven months, 1, five months, 1, four and one-half months, 1, four months, and the rest less than four months.

In 83 per cent of our simple pneumothoraces, the date of onset is known, together with the date of death or the fact that the patients were still living at the time the data were assembled. A full analysis is given in table 7.

Line 2 of table 7 shows the number of deaths during any one period, and line 3 the total deaths at the end of any period. The total deaths are 70. Of the 13 living cases which figure in this table, 1 was living five months after his pneumothorax, 2 between six months and one year, 5 between one and two years, 1 between two and three years, 1 between three and four years, and 3 over four years. Consequently, as shown in line 4, at the end of the periods from six months on, there will

be from 1 to 10 cases that we cannot figure as either dead or alive. Line 5 shows the number whom we know to have lived beyond the period given, and line 6 the total known living and known dead.

TABLE 7

1. Period	FIRST DAY	SECOND TO TENTH DAY	ELEVENTH TO THIRTIETH DAY	SECOND TO SIXTH MONTH	SEVENTH TO TWELFTH MONTH	SECOND YEAR	THIRD YEAR	FOURTH YEAR
2. Deaths during period	7	15	17	18	6	3	3	1
3. Total deaths at end of period	7	22	39	57	63	66	69	70
4. Undetermined at end of period	0	0	0	1	3	8	9	10
5. Known living at end of period	76	61	44	25	17	9	5	3
6. Total of known living and known dead at end of period	83	83	83	82	80	75	74	73
7. Per cent dying during period based on total known dead	10	21	24	26	9	4	4	1
8. Per cent dying during period, assuming no deaths in remaining cases	8	18	20.5	22	7	3.5	3.5	1
9. Per cent dying during period, assuming all remaining cases die in period in which charted	8	18	20.5	23	9.5	9.5	5	2.5
10. Mean of 8 and 9	8	18	20.5	22.5	8	6.5	4	2
11. Per cent dead at end of period based on total known dead	10	31	55	81	90	94	99	100
12. Per cent dead at end of period, assuming no deaths in remaining cases	8	26.5	47	68.5	76	79.5	83	84
13. Per cent dead at end of period, assuming all remaining cases die in period in which charted	8	26.5	47	70	79.5	89	94	96
14. Mean of 12 and 13	8	26.5	47	69	77.5	84	88.5	90
15. Per cent living at end of period based on total known living and known dead	92	73.5	53	30.5	21	12	6.5	4
16. Per cent of known living at end of period based on total cases	92	73.5	53	30	20	11	6	4
17. Per cent living at end of period presuming no deaths among living	92	73.5	53	31	24	20.5	17	16
18. Mean of 16 and 17	92	73.5	53	31	22.5	16	12	10

Death-rates in spontaneous pneumothorax are usually based on the total deaths. Line 7 shows our rates on this basis, and it is with these rates that most rates in the literature should be compared. The rates based on the total cases (line 8) are more nearly correct, but err in that they assume that all cases in line 4 lived the full four years. Line 9 like-

wise errs in that it, contrariwise, assumes pessimistically that no case lived beyond the period in which it was charted, and consequently it gives too high a death-rate. Line 10 is a mean, which probably more closely approximates the true rate. Because of the small number of cases, the differences between lines 8, 9 and 10 are immaterial.

The same difficulty in determining a true rate is shown in lines 11, 12, 13 and 14, which represent the rate of total deaths to the end of the period indicated. Line 12, like line 8, is lower than the true rate, and falsely assumes no deaths among the undetermined cases of line 4. Line 13, like line 9, assumes that all cases in line 4 failed to live beyond the period in which charted, and, consequently, gives too high a rate. Line 14 more closely represents the true rate. Lines 15, 16, 17 and 18 are comparable figures for the percentages living.

Our death-rates are much lower than most of those cited above, as evidenced by a comparison of Kahn's (2) 25 per cent on the first day with our 8 or 10 per cent, or his 50 per cent in the first week with our 26.5 or 31 per cent in the first ten days. Also, Fishberg's (27) 90 per cent in one month is to be compared with our 47 or 55 per cent, depending upon how his rates are figured.

REMAINING CASES: CONDITION

On June 1, 1925, there were 16 patients living, whose conditions, as nearly as could be ascertained, were as follows:

1. Spontaneous pneumothorax April, 1919; no operative intervention; left hospital in same year in good condition; still living, condition unknown.

2. Spontaneous pneumothorax, January 1, 1921; no operative intervention; left hospital in same year in good condition; still living, condition unknown.

3. Spontaneous pneumothorax, winter of 1920–1921; pyopneumothorax; operative intervention; now slowly dying of amyloid disease.

4. Spontaneous pneumothorax, March, 1922; pyopneumothorax; operative intervention; still draining; fair condition.

5. Spontaneous pneumothorax February 7, and May 15, 1923, on the same side; pyopneumothorax; operative intervention; still draining; fair condition.

6. Spontaneous pneumothorax, winter of 1923–1924; pyopneumothorax; operative intervention; draining; slowly retrogressing.

7. Spontaneous pneumothorax, August, 1922, and June, 1923, same side; pyopneumothorax; operative intervention; draining; retrogressing.

8. Seven cases with spontaneous pneumothorax, developing respectively in September, 1924; April, 1924; winter of 1923–1924; July, 1924; June, 1924; fall of 1922; and prior to April, 1925; none requiring operative intervention and all retrogressing.

9. Two cases developing spontaneous pneumothorax in April, 1924, and December, 1924, respectively; no operative intervention; condition good; one arrested and one inactive.

The above summary shows that two of the living cases are known to be in good condition and two more are presumed to be in good condition. All others are potentially terminal cases. The outlook, therefore, even for those cases who escape early death, is not at all bright.

PRESENCE OF FLUID

In 54 of our 102 cases the presence of fluid was noted. It is presumed that very small amounts of fluid were present in many other cases, but it is not believed that there was a failure to note the presence of fluid in amounts sufficient to be of clinical significance in more than a few cases. When the fluid changed in character it is here classified only in its final form.

In 5 cases the fluid was clear and serous (hydropneumothorax).

In 6 cases it was a tuberculous pus.

In 23 cases it was a pyogenic or mixed pus.

In 20 cases its character was either not determined or not stated.

TREATMENT

The usual symptomatic treatment was followed. In addition, in 15 cases air alone was removed. In some of these cases it was removed frequently over a period of days. Its removal was usually controlled by a manometer. In 4 other cases air and fluid were removed, and in 16 cases fluid only was removed. In 5 cases the spontaneous pneumothorax was continued as an artificial pneumothorax. In 14 cases some form of a thoracotomy was performed, and in 8 cases major thoracoplastic operations were done.

In 12 cases attempts were made to sterilize a pyopneumothorax by the use of aniline dyes, formalin or iodoform. I do not think a single case yielded more than temporary success. In most of these cases a

bronchial fistula was demonstrated during treatment. I believe that in many of these cases this treatment caused a reopening of a partly healed fistulous tract.

I believe that here, as in many other institutions, our treatment has not been aggressive enough. Kahn thinks that very few cases, if properly treated, will die of shock, suffocation or heart failure. That some will, is demonstrated by one of our recent cases, in which a needle was introduced immediately after the pneumothorax occurred, and the pleural pressure was kept continuously at minus 3 or 4 cm. of water. There was no mediastinal displacement and the lung was only partly collapsed, yet the patient died in a few days, apparently of heart failure. No fluid developed.

If the patient survives the shock of his pneumothorax, the prognosis from then on will depend very materially upon whether or not fluid forms and also upon the nature of the fluid. In our series, about half developed fluid, but many of these died so shortly after the accident that there was not time for a frank pleural effusion to develop. Probably the majority of cases living more than a few weeks will develop fluid. Four varieties of pleural fluid and their treatment may be briefly considered:

1: If the fluid is serous and free from all microörganisms, including tubercle bacilli, it has no bad prognostic import. On the contrary, it is claimed that the healing of a fistulous opening in the lung is favorably influenced by the presence of fluid. Such an effusion should be left alone unless mediastinal pressure-effects or extensive lesions in the contralateral lung demand its removal. Frequently the compressed lung will be expanded by adhesions, whose formation is obscured by the effusion, and, if it is desired to continue the spontaneous as an induced pneumothorax, it may be advisable to replace some of the fluid by air in order that this tendency to expansion may be watched for and prevented. If such a fluid is removed it should always be removed by aspiration and never by thoracotomy.

2: The fluid may be serous or semiserous and contain tubercle bacilli, but no other microörganisms; the prognosis and treatment here are not materially changed. Frequently, with this type of an effusion the patient will run an elevation of temperature for several days or weeks and, rarely, for several months. This calls for no operative intervention beyond diagnostic puncture. This tuberculous serous effusion probably exerts a beneficial influence upon the disease as a whole. These fluids will usually absorb, and they do not necessarily produce so great a thicken-

ing of the visceral pleura as to prevent a later expansion of the compressed lung. When mediastinal pressure-symptoms or serious contralateral lung disease demand the removal of the fluid, it should be removed by aspiration only, care being taken to disinfect the needle-tract by injecting iodine as the needle is withdrawn. If the effusion produces a severe and protracted fever, it may be necessary to withdraw the fluid and replace it by air, or advisable to attempt sterilization by aniline dyes, iodoform or formalin. All treatment should be through the instrumentality of the aspirating needle; thoracotomy should not be considered at this stage.

3: The fluid may be thick and purulent, but show only tubercle bacilli. This fluid alone constitutes a distinct menace to the welfare of the patient. Occasionally, so severe and prolonged a fever will result that operative measures will be indicated. Also, the visceral pleura under this purulent fluid will shortly become so thickened that a full expansion of the lung can never occur. Consequently, an attempt should be made early to change the character of the fluid by the use of aniline dyes, iodoform, etc.; and, as this will rarely yield satisfactory results, the early expansion of the collapsed lung should be encouraged by maintaining a negative pressure in the pleural cavity. All treatment should be through the aspirating needle; and, as a large-calibre needle will be necessary because of the thick fluid, special effort must be made to prevent the formation of sinuses. In some cases the size of the pleural cavity should be reduced by producing paralysis of the diaphragm of the affected side by exairesis of the phrenic nerve. If these measures fail, and it becomes evident that the patient will ultimately become an open empyema case, a complete extrapleural thoracoplasty should, if possible, be performed *before* a thoracotomy is done, hoping thereby to materially reduce the size of the open empyema cavity and at the same time permitting the major operation to be performed in a clean field.

4: The fluid may be, from the start, a mixed-infection pus (tubercle bacilli and pyogenic microörganisms). More frequently it eventuates from other forms of fluid. The prognosis in these cases is about as hopeless as can be. A few cases have been reported, in which the fluid was spontaneously evacuated through a bronchial fistula and in which the patient did fairly well. Attempts to sterilize the fluid have failed almost uniformly. In these cases one must remember that thoracotomy must be performed very soon, to relieve the sepsis. Advantage should be taken of this fact, and an attempt made to diminish the size of what is to be an open empyema by an early extrapleural thoracoplasty. If the

patient will consent, the operation should be performed as soon as the condition is recognized. I do not believe that delay, in order to attempt sterilization of the fluid, is justifiable. If a thoracotomy is first performed for the relief of sepsis, and later a thoracoplasty, the operative wound will quite probably be widely infected. Sepsis can usually be controlled by treatment through the aspirating needle for a time sufficiently long to permit of an extrapleural thoracoplasty with primary healing, and then only should a thoracotomy be done. It is evident that before a thoracoplastic operation is attempted the lung on the opposite side should be carefully observed to determine its ability to carry on the respiratory function unaided.

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ACCIDENTAL PNEUMOTHORAX[1]

CASPER F. HEGNER

Pneumothorax is always secondary to some lesion of the lung or of its enveloping structures. Mentioned in the Hippocratic writings under the term empyema, the condition was not understood. Though the presence of the fluid in the pleural cavities was recognized for centuries, the pathological presence of air was overlooked.

In 1759 Meckel (1) first clearly recognized the presence of air in the pleural space and understood the effect on respiration.

In 1803 Itard (2) gave pneumothorax its name. His work, based on studies of pneumothorax at autopsy, together with the epochal work of Laennec (3) in 1819, established pneumothorax clinically. Laennec described simple pneumothorax, pneumothorax with effusion, and pneumothorax with effusion and fistula.

In 1823 Davy (4) was the first to describe valvular pneumothorax. Bard (5) is given credit for demonstrating the positive pressure in this condition.

In 1841 Saussier (6) divided pneumothorax etiologically into traumatic and nontraumatic pneumothorax.

In 1879 Weil (7) made the first classification based on animal experiments. He listed pneumothoraces as follows:

1. *Closed:* With no pulmonary communication.
2. *Open:* With a free pulmonary communication.
3. *Valvular:* With a bronchopleural communication.
4. *Mixed:* Some combination of the above types.

Spontaneous pneumothorax, under this and many other terms, has been recognized since the middle of the nineteenth century.

Accidental pneumothorax is a term that has, however, only recently come into use. As employed in case-reports by West (8), Phalip (9), Beggs (10), Kahn (11), and others, it confuses spontaneous with accidental pneumothorax. Simon (12), in a very recent case-report, em-

[1] Read before the Medical Society of the City and County of Denver, April 20, 1926.

ploys the term accurately, and illustrates one type of accidental pneumothorax.

The danger of injuring the free lung and visceral pleura by the use of a needle in thoracocentesis has long been recognized. The danger of similar injury during the induction of artificial pneumothorax, or by the altered intrapleural tension and the increasing stress on pleuritic adhesions resulting from the injected air, is no less real. These are etiological factors in the production of several types of accidental pneumothorax.

No classification has been made of accidental pneumothorax. Since the almost universal use of induced pneumothorax in selected cases of pulmonary tuberculosis it is becoming increasingly frequent. Because of this fact, and on account of a better understanding of intrathoracic diseases and the physics of pneumothorax, I am convinced that a reclassification will clarify our concepts of pneumothorax. The following classification is therefore suggested: *1:* Traumatic. *2:* Spontaneous. *3:* Induced. *4:* Accidental.

1: Traumatic pneumothorax is secondary to external violence, with or without an opening in the chest-wall, and causing a rupture of the nondiseased visceral pleura, lung or bronchi, with escape and accumulation of air in the pleural cavity.

Crushing injuries of the chest, buffer accidents, fracture of the ribs with laceration of the visceral pleura or lung, and punctured or penetrating stab or gunshot wounds are the commoner types of violence.

The cause and effect are clear. With a nondiseased lung, the capacity for recuperation to a fully functioning lung is remarkable.

2: Spontaneous pneumothorax is secondary to some lesion or disease of the lung. It is either complete, incomplete or localized. It may develop in an apparently healthy individual, in whom the pulmonary lesion was not previously recognized. It most frequently occurs in patients with obvious pulmonary lesions, tuberculous or, less often, nontuberculous.

The most common lesions are early, small, caseating tubercles just beneath the parietal pleura, small superficial tuberculous cavities, and interstitial, marginal or superficial emphysematous blebs, not protected by pleuritic adhesions. Any sudden, even slight, increase in the intrapulmonary pressure, or a slight uneven alteration of the pleural tension, may cause rupture of the pleura and an escape of air into the pleural space. This form of spontaneous pneumothorax is usually massive or complete. The extensive collapse, though causing immediate and

severe cardiac and respiratory embarrassment, if counteracted, is favorable in its effect on the diseased lung. It puts the part at rest, leads to closure, sealing and healing of the tear, usually of the valvular pulmonary type, in the lesion of the lung. Effusion may develop. This is usually serous; but it may become seropurulent or purulent. If properly and conservatively treated, complete restitution of function is not uncommon.

Gangrene, or pyogenic or tuberculous abscess or cavity, either of which may be in direct communication with a bronchus, may erode into the pleural space. A foreign body in a bronchus or the oesophagus may perforate directly, or secondarily by suppuration (abscess or bronchiectasis) ulcerate into a free pleural space. This form of spontaneous pneumothorax is usually partial, and is always infected. The resulting fistula is of the open, bronchial type. The pneumothorax demands surgical intervention for control and cure.

Small localized spontaneous pneumothorax is sharply limited by circumscribed adhesions. Its presence may not be suspected, and it is therefore easily overlooked. It causes few, slight, or no symptoms. Physical signs are not always pronounced, but they can be elicited by careful examination. The diagnosis is usually made by X-ray.

The cause and effect of spontaneous pneumothorax are not always clear.

Whatever the predisposing factors in the lung and whatever the exciting extrapulmonary factor, *spontaneous pneumothorax develops independently of any therapeutic puncture or opening of the pleura.*

3: Induced or artificial pneumothorax follows purposeful attempts to relax or collapse a diseased lung by the repeated introduction of an increasing volume of air or gas through a therapeutic needle-puncture of the parietal pleura. The volume of air is slowly introduced through a needle penetrating the thoracic wall into a free pleural space. The alteration of the intrapleural pressure is manometrically controlled. The effect of the air in the pleural space and on the lung after each injection is, or should be, radiographically or fluoroscopically noted.

4: Accidental pneumothorax may develop during attempts at, or in the course of, induced pneumothorax or therapeutic puncture of the pleura, for the diagnosis or the amelioration of intrathoracic disease. The accessional air does not enter the pleural space through the needle, but comes from the lung or bronchi. The volume and rapidity of entering air and the alteration of the intrapleural pressure are not under direct control. The volume of air is limited only by the capacity of the pleural space. This is

determined by the site, size, number and character of the openings, the condition of the lung, mediastinum and diaphragm, and the absence or presence and extent of pleural adhesions.

Accidental pneumothorax is a hazard of artificial pneumothorax. It is truly an accident, a complication, which may, and frequently does, seriously aggravate the symptoms, as well as the disease, for the relief of which the therapeutic manoeuvre was undertaken. All too commonly it leads to the development of that most serious and intractable condition, pyopneumothorax with bronchial fistula.

Accidental pneumothorax may be: *1:* Immediate or transient. *2:* Delayed or temporary. *3:* Late or permanent.

1: Immediate: Due to puncture of the lung or damage to the visceral pleura by the therapeutic needle in a free pleural space. It is usually transient, disappearing in a few days or weeks.

2: Delayed: Developing after a lapse of hours or days, caused by the puncture and subsequent rupture of some small diseased or weakened area near the surface of the lung. It is due to a combination of the puncture and induced pressure, augmented by an increase of intrapulmonary pressure or tension and tearing of an adhesion of the pleura. It may be temporary and frequently has a valvular type of pulmonary fistula (Bard (5)). Effusion may complicate it and is serous at first, but the effusion becomes infected by pyogenic microörganisms or tubercle bacilli from the lung.

3: Late: Develops after repeated refills of gas or air, consequent to efforts to increase compression of the lung, a too rapid filling, or the introduction of too great a volume of air.

The introduced air directly or indirectly altering the equable distribution of pressure or surface tension within the pleural space, with or without an unbalanced increase in the intrapulmonary pressure, is the precipitating factor in the development of the delayed and late types of accidental pneumothorax.

Rupture takes place, through a weakened and unsupported place on the surface of the lung, at or near the base of an adhesion (Cahn (13)), near or into an abscess or cavity in direct communication with a bronchus, or through an attenuated adhesion containing a bronchiole. A permanent bronchial fistula of the open type is formed. Infection of the pleura from the lesion in the lung or from the patent bronchial fistula promptly sets in. Pyopneumothorax, either pyogenic, tuberculous or mixed, with open bronchial fistula, is established.

The most common sites of the fistula are the inferior part of the upper lobe, or the upper part of the middle or lower lobe on a plane of the third rib (Houghton (14)). It is neither in the apex of the lung, nor in the upper part of the upper lobe, where the disease is most advanced. This area is well protected by the conical shape and comparative immobility of the upper thorax, and by the usual presence of firm diffuse adhesions.

The opening, small at first, becomes larger, as a result of tension, stretching and the erosion of continued infection. It may be single or multiple.

There are factors common to both spontaneous and accidental pneumothorax. The terms are not synonymous. *The additional artificial factor of therapeutic puncture and induced pressure distinguishes the accidental type.* If we appreciate the sequence, the accidental feature will be readily understood.

The principles of the treatment of accidental pneumothorax are: *1:* Supportive measures for the acute cardiac and respiratory embarrassment. *2:* Relief and control of the excessive intrapleural pressure to a point not greater than is necessary to alleviate the urgent cardiac and respiratory symptoms. There should be substituted and maintained a low positive or neutral for a high positive pressure. A low positive pressure compresses the pulmonary lesion, places the diseased area at rest, relaxes the fistulous opening in the lung, and produces conditions favorable for its healing, and at the same time protects the pleura from additional infection from the lung (Aron (15)). *3:* Avoid, control or eliminate infection of the pleura, by repeated aspiration, supplemented by gentle injection of antiseptics. If these prove ineffectual, drainage by some modification of the closed method should be instituted. *4:* Effect closure of the fistulous opening by low positive intrapleural pressure. If after a brief trial these measures are not successful resort to surgery. Phrenicotomy, by its paralyzing effect on the diaphragm, resting the lung and relaxing adhesions, may be sufficient and should be the first surgical step. Failing to secure closure of the fistula by these comparatively minor procedures, the more radical partial or total surgical collapse is promptly indicated.

A thorough comprehension of all the factors in accidental pneumothorax is imperative; otherwise the intrathoracic conditions soon become irremediable, the symptoms grave, and the progress rapidly unfavorable.

The presence of fluid is evidence of irritation or damage to the pleura. So long as it remains serous and not excessive or controllable one should

temporize. With the development of pus one can be almost certain that infection from the lung has occurred.

Too much is usually expected from drainage. Prolonged closed drainage may be justified, but should not be replaced by prolonged open drainage. Open drainage very considerably adds to the difficulties and dangers. The resection of a part of a rib or ribs with open drainage in large empyema cavities is a delusion, and is not justified. It is not indicated. It is pernicious. One exception to this rule is presented in small empyema cavities, especially those confined to the lower segment of the chest. Here open drainage with phrenicotomy might secure ample relaxation of the walls of the cavity and permit closure of a fistula by fibrosis and contraction.

When toxic symptoms of any but mild degree supervene, or in cases with uncontrollable or open pulmonary or bronchial fistulae, immediate surgical intervention is urgently indicated. Procrastination and so called conservative measures are homicidal.

Radical surgery,—a partial or total collapse,—with concomitant closed or open drainage of the empyema cavity through an independent stab puncture, an obligatory adjunct, gives the greatest assurance of success. Radical surgery is conservative in the fullest sense of the term; it should not be considered the last resort. Favorable results cannot reasonably be expected when the pathological conditions have progressed beyond control. A profoundly toxic patient, with depleted vitality, a lowered cardiac reserve, due either to mechanical displacement of the heart in a rigid retracted mediastinum or to a toxic myocarditis, with a compromised contralateral lung; a large, rigid-walled heavily infected empyema cavity, with large single or multiple bronchial fistulae in a tubercle-riddled irretrievably contracted lung is not a surgical risk.

In a large empyema cavity with a patent bronchial fistula, the only chance for cure lies in a partial or total surgical collapse. This is a very formidable procedure. The earlier it is undertaken, the less unfavorable the intrathoracic conditions, and the better general condition of the patient, the more successful will be the result.

Concomitant drainage is an absolutely necessary requisite to surgical success. Neglect of this essential will defeat the purpose of the surgical attack by favoring the reaccumulation of pus, which will interfere with the immediate collapse, and by continued infection increase to a great degree the fibrosis and stiffening of the lung and pleura, and cause the development of a rigid residual empyema cavity that will be almost impossible to collapse by any procedure.

Bettman (16) maintains and has demonstrated the futility of attempting closure of bronchial fistulae by any surgical technique directed toward the bronchus. Bronchial fistulae close by the extension and contraction of fibrosis from the lung and pleura about the opening. This may be facilitated, under favorable circumstances, by suturing the marginal tissues over the opening.

The objectives of the surgical attack are, first, to relax the stiffened rigid area of the lung and pleura containing the opening of the fistula, and, next, to bring into contact by adequate collapse the parietal and visceral layers of the empyema cavity. This contact of the parietal with the visceral pleura, maintained by pressure, temporarily seals the opening and favors permanent closure directly, or indirectly by the fibrosis already present about the fistula. Reaccumulation of pus is made impossible by the presence of a dependent drain. Closure of the empyema cavity is usually effected by a continuing and advancing fibrotic contraction of its walls. One exception to this favorable issue occurs in tuberculous pleuritis, the most disheartening of all the conditions with which we have to contend. The best way to combat this is by converting the closed cavity into an open deep paravertebral wound and treating this by heliotherapy.

The size, shape and contour of the empyema cavity, the condition and topography of the lung, and the presence, location and character of the pleuritic adhesions can be determined only by careful study of the physical signs, combined with radiography of the chest. Radiographic deductions can be greatly enhanced by the injection of some opaque, preferably fluid medium, of which sodium iodide, 12 per cent, is a prototype.

With this information the number and length of the ribs to be resected can be estimated. These should be sufficient in number and length to go wide of the known extent of the empyema cavity, in order to mobilize the known upper and other marginal limits, and to relax adhesions.

Drainage should be provided in the most dependent part of the cavity. Compression by suitable elastic dressings and bandages should be maintained until contraction of the cavity is firm and complete.

The prognosis depends upon the condition of the collapsed lung, the functional capacity of the opposite lung, and the cardiovascular reserve. The suddenness of onset and the degree of involvement are of greatest moment in the early phase of pneumothorax. After the initial phase the greatest danger is not due to the presence of air or to its mechanical

effect, but to the inevitable sepsis consequent to infection from the lung or bronchial fistula. The ability to control the intrapleural pressure, to close the fistulous opening and to eliminate the consequent infection most favorably influences the outlook.

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PULMONARY ABSCESS FOLLOWING ABORTION

LEROY S. PETERS

The following case history may be rare enough to warrant a brief report:

The patient was admitted to the Methodist Sanatorium, Albuquerque, September 21, 1925, with the following history:

Female, age 27; married; average weight 114; highest weight 126, eight years ago; has had two children, one stillborn, the other lived two days, born nine and five years ago, respectively.

Family history negative for tuberculosis.

Past History: Always well up to three years ago, when she began to feel run down in general health. Tired easily on exertion, extremely nervous, and noted a low-grade fever averaging 99.2° in the afternoon. In June, 1925, had operation under general anesthetic for obstruction of the intestines. There was no evidence of intestinal or peritoneal tuberculosis at operation. After this she developed a slight cough and slight amount of sputum. Never had a hemorrhage but has spit "color," so she says.

Present Condition: Patient looks well, although slightly under normal weight and slightly anemic; weight 109; height 64 inches; temperature 99.2° daily; pulse normal; cough slight; sputum slight and negative for tubercle bacilli; appetite fair. Complains of pain in abdominal tract and a great deal of gas. Bowels constipated but occasionally loose. Sleeps well.

General Examination: Ears, nose, pharynx and larynx negative. Lymph nodes not palpable. *Chest:* Lungs negative except for harsh vesicular breathing over both lungs and few râles over left base posteriorly. Heart normal. *Abdomen:* Negative, except at times there is some evidence of gas, especially in region of stomach. *Extremities:* Negative.

Laboratory Reports: Sputum negative for tubercle bacilli; urine normal.

X-Ray Findings: Chest: Trachea, heart and diaphragmatic shadows normal. The peribronchial lymphatic areas are very much thickened. The upper bronchial tree on left side shows definite beading. Beading also of lower tree on right. The apices, periphery and bases of lungs are clear. Gastrointestinal series negative.

The subsequent history differs little. The patient was put on usual routine for tuberculosis, although I could never make up my mind to a positive diagnosis. Graduated exercise was worked up slowly, and sun-baths for the abdominal symptoms left the patient showing gradual improvement. About March 1, 1926, the patient found herself pregnant and consulted me for therapeutic abortion. This was not necessary from the standpoint of her lung condition, but she feared having a baby and went to another physician, who did a curettement, March 22, under local anesthesia. Three days later her fever went to 104°, and the physician did a second curettement. The fever continued to run high, 102° to 103°, for ten days, when she returned to the sanatorium and sent for me. Physical examination of the chest revealed nothing except a few pleural râles over the right base. She complained of pleurisy over this area. The temperature continued to run from 101° to 103° for two weeks after her return to the sanatorium. I called the physician who did the abortion, and examination revealed nothing to account for the fever. The patient began spitting "color" at the end of two weeks from the time of operation, and I made a diagnosis of probable broncho-

pneumonia. After three days of blood-tinged sputum pus began to appear in great quantities, blood-streaked, foul-tasting and foul-smelling. Then the diagnosis of abscess was apparent, and was confirmed by X-ray. The quantity of pus averaged 500 cc. daily, but with postural drainage dropped in two weeks to nothing. Apparently the patient has recovered without operation.

In view of this history there can be no doubt that this abscess was a result of a thrombus which lodged in the lung.

The abscess area can be seen readily in the radiograph taken after the drainage started. The radiograph of the chest prior to the abscess is

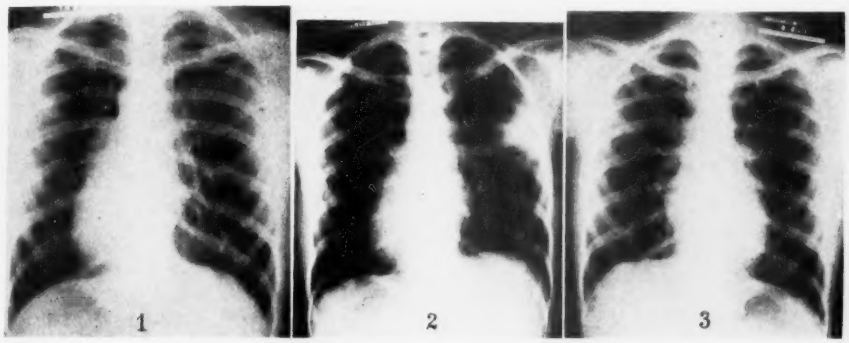

FIG. 1. CHEST BEFORE FORMATION OF ABSCESS
FIG. 2. SHOWING ABSCESS AT THIRD RIB NEAR PERIPHERY OF LUNG
FIG. 3. LUNG CLEAR AFTER THREE WEEKS OF POSTURAL DRAINAGE

also shown. A recent radiograph after three weeks on postural drainage shows the lung picture to be practically the same as before the formation of the abscess.

I wish to thank Dr. J. R. VanAtta for the series of radiographs in this case.

Note: Since writing the above report, Dr. VanAtta autopsied a woman, dead following abortion, and found two living infarcts. Death had occurred too soon for abscess formation.

Corrections

In the paper by Austrian and Willis, *The Pulmonary Effects of Intratracheal Injections of Tubercle Bacilli and Blood in Rabbits*, September, pp. 306-316, the following corrections should be made:

Page 310, at the end of the first paragraph add: "Tuberculous rabbits, injected intratracheally with tubercle bacilli in physiological salt solution, developed pulmonary foci identical with those that followed similar injections of tubercle bacilli suspended in blood."

Page 314, line 3: For "suspension of tubercle bacilli in blood" read "suspension of tubercle bacilli in physiological salt solution."

REMARKS ON THE COÖPERATION OF SCIENCE AND PRACTICE IN TUBERCULOSIS[1]

THEOBALD SMITH

It falls to my lot—and it is a highly honorable and agreeable task—to welcome our guests from abroad and from our own Continent on behalf of our host, the National Tuberculosis Association of the United States. We are grateful to all our foreign guests for the efforts they have made to come and confer with us. We sympathize with the loneliness of the traveller and realize the pull of the work left behind and undone. We trust, however, that when you return home there will have accumulated a considerable balance of improved health, of renewed stimulus, to face the daily tasks, and perhaps of new ideas gained on the way. It is needless to say that we greatly regret the unavoidable absence of some of our distinguished members who, we were led to believe earlier in the year, had decided to take part in the deliberations. Various incidents and untoward events have conspired to deprive us of their stimulating presence and their active coöperation in making our deliberations even more successful than they promise to be.

There is an advantage in that we have before us a definite, compact, even though highly complex subject. We do not need to discuss what tuberculosis is and what it is not. The grasp we have upon the tubercle bacillus relieves us of formulating a platform for discussion. There is complete unanimity as to the object in view. We are here to devise new and strengthen old defenses against the tubercle bacillus. While we may differ as to methods of offense and defense in minor particulars, there can be no question of our unanimity on the guiding motive. We are assured by the history of science that our differences will be ironed out by our successors in time, and that the final results cannot be successfully disguised by propaganda, negatived by legal enactments, or exploited for personal gain. The truth will come to light. Whatever is accomplished is for the benefit of humanity in its broadest dimensions. Without differences of opinion as to interpretation, modes of approach

[1] Address of the President, at the opening of the Fifth Conference of the International Union Against Tuberculosis, Washington, D. C., September 30, 1926.

and end-results, our sessions would be quite uninteresting. It is they that stimulate thought, lead to review and revision of our own concepts, and tend to build a firmer foundation for those who follow us in this work.

It is 18 years ago that some of us here present met in this city during the International Congress on Tuberculosis. It was a large and enthusiastic gathering and it left its activities recorded in several large volumes of proceedings. Among the important problems still agitating the members at that time was the relation between human and animal tuberculosis, and it was our good fortune to have as one of our distinguished guests Robert Koch, whom we could meet face to face and ply with questions *ad libitum* to bring out his point of view. Since that time, the debatable differences of opinion have been smoothed out, and we are now concerned only as to the most conservative and economical means for making that residuum of danger lurking in bovine tuberculosis for our young and less resistant population as harmless as possible.

Many other changes have come about since then. Those of us, who, as amateurs are interested in outdoor life and in the forests, find sooner or later that the care of forests means the care of individual trees in the last resort. So the mass-movement against tuberculosis started by the discovery of the tubercle bacillus, and led by the laboratories, has gradually become a movement for the study and rehabilitation of the individual patient. The laboratory has for the time being taken second place. It is an important aid, without which definite progress would be impossible, but the laboratory has also from time to time led us astray by dangling before us new and startling cures. The only remedy for such failures is the closest coöperation between the experimental laboratory and clinical medicine.

The hope and expectation that some all-inclusive remedy may be found need not be given up, although the object of attack is multiform in character. All slow, insidiously developing, chronic diseases are multiform. We need but to mention syphilis and leprosy. Each infectious disease is unique, and gives us startlingly little information concerning many others. It seems that we must start from the very beginnings with each specific disease. Nevertheless it is not improbable that, if a useful remedy comes, it will arrive unexpectedly from sidelines, where some other disease has furnished the clue. While we are patiently awaiting the arrival of this most welcome guest, our hope to-day rests in preventive measures, which see to it that the human

being, from birth on, inhales or ingests as few virulent bacilli as possible, and that the individual and the family be made as strongly defensive, through a proper environment, as the available world energy will permit.

The curve of attainment, which rises so precipitously at the beginning of a great epoch, like that with its origin in the discovery of the tubercle bacillus, soon changes its slope toward a dead level, when we must work simply to hold what has been accomplished by those who have preceded us. Or, to put it in another way, we are now working in the heat of the day; the freshness of the morning is gone. Renewed courage is needed to do the quiet, unobtrusive work, which is eventually turned to account by some crowning, but no more essentially important work. It is meetings like the present from which we must draw the inspiration and the stimulus, and learn the path to follow for the next few years

TUBERCULOSIS HOSPITALIZATION IN THE UNITED STATES[1]

RESULTS, TYPES OF CASES, FACILITIES AND COSTS

A Preliminary Survey

GODIAS J. DROLET[2,3]

The growth of the tuberculosis sanatorium movement in the United States, after the successful demonstration of the open-air and rest treatment by Dr. Trudeau, has been marked, and of late years, under the added impetus and support given by the tuberculosis associations throughout the country, has been one of continuous development. From data secured by the National Tuberculosis Association the writer has assembled information on the dates of opening of 536 sanatoria and tuberculosis hospitals, with facilities for the treatment of 63,338 patients. The institutions include practically all the recognized ones in this country.

As Knopf has already reminded us, the first institution devoted to the exclusive treatment of the consumptive poor in the United States was the Channing Home in Boston, opened in 1857. In the same year the first private sanatorium was established in Asheville, North Carolina, by Gleitsman. In 1884 Trudeau founded the famous Adirondack Cottage Sanitarium; and in 1890 Bowditch established near Boston, without seeking special climatic advantages for the location of the institution, the Sharon Sanatorium.

In 1895 there were already in this country 19 tuberculosis sanatoria or hospitals, with a capacity of 1,450 beds. In 1900 there were 34 institutions and 4,485 beds available. In 1905 there was a total of 67 sanatoria and tuberculosis hospitals with 9,000 beds. Between 1905 and 1910, seventy-eight other institutions with 11,195 beds were added. Between 1910 and 1915, one hundred and thirty-two were opened with a capacity of 15,000 beds. Between 1915 and 1920, one hundred and

[1] An address given at the Twenty-Second Annual Meeting of the National Tuberculosis Association, Washington, D. C., October 5, 1926.

[2] Statistician, New York Tuberculosis and Health Association.

[3] With acknowledgments to L. M. Dorr and E. S. Davies for assistance in this investigation.

thirty tuberculosis institutions were opened, adding 13,400 beds. Since 1920 another 129 institutions have been opened, with a capacity of 14,557 beds. Furthermore, there are several other public institutions

TABLE 1

*Tuberculosis mortality in the United States since 1900**

YEAR	POPULATION (a)			TUBERCULOSIS (c)		
	Registration area		Entire United States (b)	Deaths in registration area	Death-rate per 100,000	Deaths in United States (d)
	Number of inhabitants	Per cent in area				
1900	30,765,618	40.5	76,129,408	62,096	202	153,781
1901	31,370,952	40.3	77,747,402	61,767	197	153,162
1902	32,029,815	40.4	79,365,396	59,083	185	146,826
1903	32,701,083	40.4	80,983,390	61,640	189	153,059
1904	33,345,163	40.4	82,601,384	66,921	201	166,029
1905	34,052,201	40.4	84,219,378	65,478	192	161,701
1906	41,983,419	48.9	85,837,372	75,648	180	154,507
1907	43,016,990	49.2	87,455,366	76,759	179	156,545
1908	46,789,913	52.5	89,073,360	78,409	168	149,643
1909	50,870,518	56.1	90,691,354	81,835	161	146,013
1910	53,831,742	58.3	92,267,080	86,309	160	147,627
1911	59,183,071	63.2	93,682,189	94,205	159	148,955
1912	60,359,974	63.5	95,097,298	90,360	150	142,646
1913	63,200,625	65.5	96,512,407	93,421	148	142,838
1914	65,813,315	67.2	97,927,516	96,903	147	143,953
1915	67,095,681	67.5	99,342,625	98,194	146	145,040
1916	71,349,162	70.8	100,757,735	101,396	142	143,076
1917	74,984,498	73.4	102,172,845	110,285	147	150,194
1918	81,333,675	78.5	103,587,955	122,249	150	155,381
1919	85,166,043	81.1	105,003,065	106,985	126	132,304
1920	87,486,713	82.2	106,418,175	99,916	114	121,317
1921	88,667,602	82.2	107,833,284	88,135	99	106,755
1922	93,241,643	85.3	109,248,393	90,452	97	105,971
1923	96,986,371	87.6	110,663,502	90,732	94	104,024
1924	99,030,494	88.4	112,078,611	89,724	91	101,992

* Compiled from *Mortality Statistics, United States Census Bureau*, by Research Service, New York Tuberculosis and Health Association.

(a) Estimated mid-year population.

(b) Continental United States.

(c) All forms of tuberculosis.

(d) Estimated by applying death-rate of Registration Area to population in entire country.

which have been authorized for construction, and some of the more popular sanatoria are still being enlarged. There is also a tendency to add children's sections in certain places.

TUBERCULOSIS IN THE UNITED STATES

To realize better the utility and necessity of tuberculosis hospitalization, the writer has brought up to date the series of figures presented last year in his study of *Recent Changes in Leading Causes of Death and Their Bearing on Tuberculosis Hospitalization*,[4] and would draw attention to the following:

First, tuberculosis mortality in 1924 in the Registration Area, which includes 88 per cent of the entire population, was at a rate of 91 per 100,000; and this would indicate that, if the same rate prevailed in the remainder of the country, we still had that year 101,992 deaths. The details annually since 1900 may be studied in table 1.

Second, as may be studied in table 2 which shows the leading causes of death in the United States in 1924, it will be seen that tuberculosis, with approximately 100,000 deaths a year in the entire country, now occupies fifth place; whereas in 1910 it was first, causing 150,000 deaths a year when the population was twenty million less.

Third, tuberculosis sanatoria and hospitals are utilized, of course, for more than merely making the dying comfortable, and the number of beds needed still falls far short of the total living cases. Significant figures are already available for a study of the present tuberculosis morbidity. For instance, from the *Reports* of the United States Public Health Service we have assembled the figures of registration for such parts of the country as were obtainable. In 23 States and 11 cities, with a total population of 64,747,088, we find that in 1924 a total of 108,662 tuberculosis cases were reported, at a ratio, therefore, of 1.81 cases per each tuberculosis death in these places and of 1.68 per 1,000 inhabitants. These figures of tuberculosis registration, which cover more than one-half of the population of the United States, tell us that there are registered annually 188,000 cases. And, of course, we also know tuberculosis registration to be an understatement, as in certain places the recorded cases are barely equal to the number of deaths. On the other hand, we notice in certain larger centres of population, for instance in New York State, that in 1924, 21,266 tuberculosis cases were reported against a mortality in the same year of 10,295; in Illinois, 15,041 cases and 5,581 deaths; in Massachusetts, 6,322 cases and 3,508 deaths; in

[4] *Transactions of the Twenty-First Annual Meeting, National Tuberculosis Association, 1925, p. 463.*

TABLE 2

*Leading causes of death in the United States**

Year 1910

(United States population: 92,267,080)

RANK	1910 LIST NUMBER	CAUSE OF DEATH	REGISTRATION AREA		DEATHS IN ENTIRE UNITED STATES‡
			Deaths	Rate†	
1	28–35	Tuberculosis, all forms	86,309	160	147,627
2	77–80	Diseases of the heart	85,489	159	146,705
3	91, 92	Pneumonias	79,524	148	136,555
4	1, 104, 105	Typhoid, diarrhea, enteritis	75,853	141	130,097
5	119, 120	Nephritis, acute and chronic	53,330	99	91,345
6	64, 65, 81	Cerebral hemorrhage, softening of brain, diseases of arteries	52,424	97	89,499
7	164–186	Accidents, homicides	48,606	90	83,040
8	150–153	Malformation, debility, early infancy	47,386	88	81,195
9	39–45	Cancer	41,039	76	70,123
10		Other causes	235,452	438	404,130
		All causes	805,412	1,496	1,380,316

Year 1924

(United States population: 112,078,611)

RANK	1921 LIST NUMBER	CAUSE OF DEATH	REGISTRATION AREA		DEATHS IN ENTIRE UNITED STATES‡
			Deaths	Rate†	
1	87–90	Diseases of the heart	176,671	178	199,500
2	74, 83, 91	Cerebral hemorrhage, softening of brain, diseases of arteries	115,219	116	130,011
3	100, 101	Pneumonias	97,403	98	109,837
4	43–49	Cancer	91,138	92	103,112
5	31–37	Tuberculosis, all forms	89,724	91	101,992
6	128, 129	Nephritis, acute and chronic	88,863	90	100,871
7	175–203	Accidents, homicides	84,165	85	95,267
8	159–163	Malformation, debility, early infancy	77,653	78	87,421
9	1, 113, 114	Typhoid, diarrhea, enteritis	41,159	42	47,073
10		Other causes	311,995	316	354,168
		All causes	1,173,990	1,186	1,329,252

* Compiled from *Reports, United States Census Bureau*, by Research Service, New York Tuberculosis and Health Association.

† Death-rate per 100,000 population.

‡ On basis of rate in Registration Area applied to entire population of continental United States.

TABLE 3

Tuberculosis registration in twenty-three states and eleven cities

PLACE	CASES REPORTED IN 1924	DEATHS IN 1924	POPULATION 1924
States			
Alabama	2,414	2,384	2,445,551
California	9,663	6,023	3,913,236
Colorado	2,585	1,600	1,004,803
Connecticut	1,736	1,221	1,503,869
Delaware	368	255	232,590
Dist. Columbia	1,330	559	486,936
Florida	1,522	1,054	1,068,520
Illinois	15,041	5,581	6,877,737
Kansas	2,554	791	1,805,555
Maryland	3,125	1,851	1,521,190
Massachusetts	6,322	3,508	4,077,599
Michigan	5,570	2,953	4,066,223
Minnesota	4,441	1,705	2,531,473
Mississippi	3,508	1,840	†1,790,618
Montana	672	414	629,003
Nevada	64	49	†77,407
New Jersey	4,938	2,997	3,442,695
New Mexico	1,105	750	375,669
New York	21,266	10,295	10,974,642
Ohio	7,039	5,080	6,219,330
Oregon	723	568	834,665
Rhode Island	495	568	633,036
Washington	2,202	2,183	1,456,106
Wisconsin	1,972	1,697	2,770,291
Cities			
Atlanta	420	285	227,710
Erie, Pa	230	99	112,571
Fort Worth	112	61	148,107
Kansas City, Mo	553	329	359,650
Louisville	743	296	258,465
Memphis	767	319	172,276
Nashville	312	210	123,424
New Orleans	1,118	692	409,534
Oklahoma	75	60	104,080
Philadelphia	*3,569	*1,777	1,951,076
Scranton	108	85	141,451
States and cities	108,662	60,139	64,747,088

Note: Living cases for each death = 1.81.

Living cases per 1000 inhabitants = 1.68.

Indicating among the 112,078,611 inhabitants in entire United States 188,292 known cases.

Compiled from *Reports, United States Public Health Service,* by Research Service, New York Tuberculosis and Health Association.

* For pulmonary tuberculosis only.

† Population, January 1, 1920.

California, 9,663 cases and 6,023 deaths; and in Ohio, 7,039 cases and 5,080 deaths.

In the single year of 1924, therefore, in the United States almost 190,000 cases of tuberculosis were reported which, we should recall, undoubtedly added themselves to another large number of old cases from previous years. With 73,715 beds, we are then still a long way from the goal of having a sufficient number for all the tuberculous, though without question a great proportion of the very sick are at present being cared for. The tuberculosis registration figures in the States and cities referred to are shown in table 3.

PRESENT INSTITUTIONAL FACILITIES

After considering, as far as known, the extent of the tuberculosis situation in the United States, we can now study more usefully the record of the present facilities and of remaining obvious needs.

According to the latest list[5] of sanatoria and hospitals made by the National Tuberculosis Association, we see that in the 48 States and the District of Columbia there is now a grand total of 73,715 tuberculosis beds available, 53,510 being for civilians, 5,479 for the insane in state institutions, 1,325 for prisoners in various penal institutions, and 13,401 for those under the care of the Federal government through the Veterans' Bureau, the Army and Navy departments, or for Indians.

The number of beds available in each State is shown on table 4, where they have been contrasted at the same time with the number of tuberculosis deaths. We have also figured there, on the basis of a bed for each death, the shortage remaining or the excess of beds in certain older communities as well as in health resorts. From this comparison we find that there is still a shortage in the United States of more than 25,000 beds. In only 11 States are there sufficient tuberculosis beds, according to this rule.

There are several States where more than 1,000 beds are still needed. Among these should be mentioned Alabama, Arkansas, Florida, Georgia, Indiana, Kentucky, Louisiana, Mississippi, Missouri, Ohio, Pennsylvania, South Carolina, Tennessee and Virginia,—most of them, as may be noticed, in the South. Furthermore, in many States the shortage existing would be considerably higher were we to remove, as not available

[5] January 1, 1926.

TABLE 4

*Tuberculosis deaths and beds in the United States**

STATE	POPULATION JULY 1, 1924	TUBERCULOSIS DEATHS 1924 (a)	TUBERCULOSIS BEDS					SHORTAGE (−) OR EXCESS (+) OF BEDS OVER DEATHS
			For civilians (b)	For insane (b)	For prisoners (b)	Federal patients (c)	Total available	
Alabama	2,445,551	2,384	172	99	100	202	573	−1,811
Arizona	394,331	1,296	466	20	10	1,068	1,564	+268
Arkansas	1,834,596	1,539	358	0	0	0	358	−1,181
California	3,913,236	6,068	3,522	250	29	1,076	4,877	−1,191
Colorado	1,004,803	1,639	2,092	55	30	2,000	4,177	+2,538
Connecticut	1,503,869	1,230	1,072	142	5	500	1,719	+489
Delaware	232,590	266	82	0	0	0	82	−184
Dist. Columbia	486,936	559	285	.....	.....	170	455	−104
Florida	1,068,520	1,057	26	24	0	0	50	−1,007
Georgia	3,028,728	2,676	295	227	70	40	632	−2,044
Idaho	481,125	219	0	0	0	170	170	−49
Illinois	6,877,737	5,642	3,240	425	162	230	4,057	−1,585
Indiana	3,036,775	2,575	910	0	20	80	1,010	−1,565
Iowa	2,487,106	1,006	681	223	8	80	992	−14
Kansas	1,805,555	787	171	83	11	0	265	−522
Kentucky	2,475,370	2,961	375	253	40	374	1,042	−1,919
Louisiana	1,864,385	2,102	253	44	20	400	717	−1,385
Maine	779,900	533	462	40	0	23	525	−8
Maryland	1,521,190	1,847	1,171	149	40	0	1,360	−487
Massachussetts	4,077,599	3,513	3,251	462	100	0	3,813	+300
Michigan	4,066,223	2,966	2,142	242	50	0	2,434	−532
Minnesota	2,531,473	1,709	2,084	0	0	388	2,472	+763
Mississippi	†1,790,618	1,906	526	0	0	0	526	−1,380
Missouri	3,455,376	3,105	1,020	0	0	0	1,020	−2,085
Montana	629,003	434	150	0	0	211	361	−73
Nebraska	1,344,652	477	168	57	12	0	237	−240
Nevada	†77,407	49	0	0	0	90	90	+41
New Hampshire	448,882	333	225	28	8	0	261	−72
New Jersey	3,442,695	2,961	2,227	186	34	0	2,447	−514
New Mexico	375,669	750	732	0	0	885	1,617	+867
New York	10,974,642	10,407	9,366	1,348	200	870	11,784	+1,377
North Carolina	2,722,669	2,773	1,278	75	48	1,081	2,482	−291
North Dakota	679,232	240	156	0	0	20	176	−64
Ohio	6,219,330	5,093	2,120	0	0	386	2,506	−2,587
Oklahoma	2,200,307	1,286	427	0	0	240	667	−619
Oregon	834,665	593	310	60	0	0	370	−223
Pennsylvania	9,208,986	7,533	4,266	400	52	177	4,895	−2,638
Rhode Island	633,036	568	595	0	0	0	595	+27
South Carolina	1,761,746	1,781	313	70	0	0	383	−1,398
South Dakota	660,956	302	240	6	5	60	311	+9
Tennessee	2,408,846	3,547	814	150	150	1,100	2,214	−1,333
Texas	5,018,602	3,398	1,830	236	70	702	2,838	−560

TABLE 4—*Concluded*

STATE	POPULATION JULY 1, 1924	TUBERCULOSIS DEATHS 1924 (a)	TUBERCULOSIS BEDS					SHORTAGE (−) OR EXCESS (+) OF BEDS OVER DEATHS
			For civilians (b)	For insane (b)	For prisoners (b)	Federal patients (c)	Total available	
Utah	484,639	183	15	0	0	0	15	−168
Vermont	†352,428	287	142	25	0	0	167	−120
Virginia	2,423,942	2,719	960	68	20	0	1,048	−1,671
Washington	1,456,106	1,087	695	0	0	270	965	−122
West Virginia	1,576,143	1,297	444	32	31	0	507	−790
Wisconsin	2,770,291	1,792	1,381	0	0	508	1,889	+97
Wyoming	216,853	104	0	0	0	0	0	−104
United States	112,085,319	99,579	53,510	5,479	1,325	13,401	73,715	−25,864‡

* Compilation by Research Service, New York Tuberculosis and Health Association.

† Population, January 1, 1920.

‡ Total local deficiency of beds amounts to 32,640, but is offset by an excess of 6,776 beds over the local requirements, especially in the health resorts, leaving a net number of 25,864 tuberculosis beds still lacking in the United States.

(a) Deaths from all forms of tuberculosis gathered from *Reports of the Census Bureau* for thirty-seven states and from the United States Public Health Service for the remainder.

(b) Tuberculosis beds available in special hospitals and sanatoria, or set aside in general hospitals and state institutions for insane and prisoners, according to the 1926 *Directory of the National Tuberculosis Association.*

(c) Beds available for Veterans, Army, Navy and Indians.

for local residents, several important Federal institutions which figure in this study.

Then, again, in certain communities where they might well afford more and find it an investment in saving lives, we should not wish to have it accepted too complacently that only one bed is needed for each death. For instance, there are sections of the country where morbidity is higher than elsewhere, or where cases run a more acute course and are in greater need of institutional facilities. Again, the figuring of beds on the basis of mortality ignores the fact that nowadays we ought to be able to find cases in the earlier stages of the disease and that sanatorium treatment in the country, instead of hospital care in the city, is in continued and increasing demand. We may, therefore, well need yet a still greater number of sanatorium beds for the more timely treatment of favorable cases.

RESULTS OF SANATORIUM WORK

All the benefits derived from the work of sanatoria are not readily appraised, but three lines of public service that they render are usually

acknowledged: *First,* that of serving as schools to educate patients suffering from a communicable disease to protect themselves, their families, and the public. *Second,* to serve as special and proper places for securing, in every way possible, the recovery of the health of those attacked by tuberculosis, or if this be no longer attainable to give them the best humane care in their dying moments. And, *third,* to protect the community by serving as places for the segregation of foci of infection.

The writer has attempted in a preliminary survey to ascertain the magnitude of these outstanding services. A questionnaire, listing certain points in sanatorium work, was sent out, and replies were received from 226 institutions, many of them the largest in the land, that have a total bed capacity of 39,500. As there are now 73,715 tuberculosis beds available in the United States, the information obtained in this survey is based on a sample of more than 53 per cent of the known tuberculosis bed facilities in the United States. Not all had records available on each of the fourteen points inquired into, but the great majority replied. (For summary of findings see table 5.)

Two hundred and four institutions, answering the question on the total number of patients admitted since their opening to July 1, 1926—and in many cases they had only an incomplete record,—furnished figures which showed that they had received 660,195 patients; and, on the

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Footnotes to Table 5.

* Summary of a survey in each State, made as of July 1, 1926, by G. J. Drolet, statistician, New York Tuberculosis and Health Association.

† Estimated for the 73,715 tuberculosis beds in the United States from the proportion which the number of beds in the institutions replying bore to the grand total.

‡ Children under sixteen years of age.

§ Term "last year" applies to either calendar or fiscal year; generally to year 1925.

(a) Several institutions had only a partial record of their total admissions since their opening, years ago; the figures given are therefore an understatement.

(b) Average cost of buildings and grounds per bed was $3, 761.

(c) Maintenance cost for "last year, calendar, or fiscal" was $1,125 per patient, or $21.60 a week per bed in use.

(d) Differences between 89,310, 89,368, and 91,319 in the estimates for the entire United States in the number of tuberculosis patients discharged "last year" arise from the fact the institutions whose reports were utilized did not all report equally on the same questions. Obviously, however, 90,000 tuberculosis patients may be agreed upon as the total number discharged a year.

(e) Scattered cases of "hilum tuberculosis" were reported in two or three institutions receiving children, particularly in New England.

(f) Stage of disease on admission of pulmonary cases discharged "last year."

(g) Condition on discharge of all tuberculosis cases, pulmonary and nonpulmonary, terminated "last year."

TABLE 5

*Tuberculosis hospitalization in the United States**

ITEMS	INSTITUTIONS REPORTING	BEDS REPRESENTED	TOTAL NUMBER FOR ITEM CONSIDERED SINCE OPENING OR "LAST YEAR"§	
			Among institutions reporting	In entire United States†
Admissions, new and old, since opening (a)	204	35,700	660,195	1,362,600
Readmissions up to July 1, 1926	132	23,100	40,105	128,500
Deaths in institution since opening	188	31,800	93,370	216,400
Replacement value of buildings, grounds (b)	177	29,446	$110,745,079	$277,000,000
Maintenance cost during last year (c)	198	32,073	$36,096,025	$83,000,000
Patient Census, July 1, 1926	221	38,726	32,529	61,920
Men (56 per cent)	221	38,726	18,293	34,676
Women (30 per cent)	221	38,726	9,643	18,576
Children‡ (14 per cent)	221	38,726	4,593	8,668
Capacity of institutions	221	38,726	38,726	73,715
Length of stay, cases terminated "last year"§	160	26,003	33,828	95,898
Under one month (17 per cent)	160	26,003	5,777	16,377
One to three months (24 per cent)	160	26,003	8,199	23,243
Three to six months (22 per cent)	160	26,003	7,328	20,774
Six to nine months (16 per cent)	160	26,003	5,511	15,623
Nine months or more (21 per cent)	160	26,003	7,013	19,881
Patients discharged "last year"	206	37,208	51,830	102,680
Tuberculous (88 per cent)	206	37,208	45,080	(d) 89,310
Not tuberculous (11 per cent)	206	37,208	6,003	11,890
Doubtful (1 per cent)	206	37,208	747	1,480
Tuberculosis cases discharged (1925)	189	31,571	39,112	(d) 91,319
Pulmonary cases (95 per cent)	189	31,571	36,842	86,019
Non-pulmonary (5 per cent) (e)	189	31,571	2,270	5,300
Stage of disease on admission (f)	176	29,742	34,686	85,960
Incipient (16 per cent)	176	29,742	5,567	13,800
Moderately advanced (34 per cent)	176	29,742	11,664	28,900
Far advanced (50 per cent)	176	29,742	17,455	43,260
Condition on discharge, tuberculosis cases (g)	184	31,581	38,288	(d) 89,368
Disease arrested (15 per cent)	184	31,581	5,544	12,940
Quiescent or improved (42 per cent)	184	31,581	16,153	37,704
Unimproved (23 per cent)	184	31,581	8,886	20,740
Died (20 per cent)	184	31,581	7,705	17,984

basis of the proportion in the United States they represent, it is astonishing to find, after the removal of 128,500 cases reported to have been included as readmissions, a probable total number of 1,234,000 different individuals received by the institutions of the entire country. Any one who has come in contact with patients returning from sanatoria knows that they are most keen in their appreciation of hygienic living, and credit for promoting practical health education must first be given to the sanatoria. In the comparatively short period since these institutions have opened their doors they have received and retrained in health one million, two hundred thousand people.

Regarding the public service of removing dangerous foci of infection from the community, I must draw attention to the dying consumptive, gasping and choking with expectoration which, in his weakened stage, he is practically unable to care for correctly. One hundred and eighty-eight institutions replied that they had cared for 93,370 patients at their death. And, on the basis of the proportion they represent of the total, it may be figured that in the United States the tuberculosis sanatoria and hospitals have already cared for more than 209,000 dying patients, as well as assisted in removing these centres of possible infection from that many homes.

UTILIZATION OF PRESENT FACILITIES

In this survey made during the summer of 1926 it was necessary to take the census of patients in the institutions as of July 1, and time and season should be borne in mind in appreciating the present use of sanatoria in the United States.

In 221 institutions, with a capacity of 38,726 beds, it was reported that on July 1, 1926, there were 32,529 patients and, therefore, that 84 per cent of the beds were in use. Of the total number utilized, 18,293 or 56 per cent, were filled by men; 9,643, or 30 per cent, by women; and 4,593, or 14 per cent, by children. These proportions of the distribution and use of the beds would indicate for the entire number of institutions in the United States that on July 1, 1926, there were in sanatoria and hospitals 34,676 men, 18,576 women, and 8,668 children, or a grand total of 61,920 patients.

This 1926 summer census of sanatoria and hospitals would indicate that 16 per cent of the beds were vacant. We should recall that a similar survey taken on March 1, 1925, which, as is well known, is the

peak of the year for sickness, showed instead that the beds throughout the country averaged 90 per cent in use and only 10 per cent vacant. The census varies, of course, for certain groups of institutions, and in fact may well indicate the tendency of the day as to the demand for tuberculosis beds. For instance, 12 sanatoria, of some 5,000 bed capacity, were 97 per cent full on July 1, 1926, whereas 10 hospitals, many of them located in town, were instead only 82 per cent in use. Is it not true that at present some of the tuberculosis hospitals in cities are apt to be older institutions, mere homes without resident physicians and modern care, as compared with the better located and managed modern sanatoria in the country?

It is to the country, in a sanatorium, that a patient wants to go, where undoubtedly he has a better chance for recovery, rather than in the old hospital. In fact, in several of the sanatoria here studied there was an actual excess in the use of their beds and the few vacancies in the others were merely during the process of turning over admissions and discharges.

In the present use of sanatoria it is interesting to note at this time that the few private sanatoria studied had 99 per cent of their beds in use. Ten public sanatoria, as compared with these private institutions, had 96 per cent of their beds in use. At present it seems that in most sanatoria, whether they be public or private or municipal, in contradistinction to hospitals, a high percentage of the beds is being used. This is strikingly noticeable in the case of the large state institutions, which are generally modern, up-to-date plants.

The United States Veterans' Bureau has had the kindness to furnish many interesting details concerning their institutions. On July 1, 1926, in 18 hospitals with a capacity of 7,252 beds, only 5,013, or 69 per cent were in use, the greatest number of vacancies being at present in a Southern institution undoubtedly less desirable for use at this warmer time of the year.

INSTITUTIONAL COSTS

The great economic loss caused by tuberculosis can in part be appreciated from a consideration of the money cost of the sanatoria and their maintenance. One hundred and seventy-seven institutions, with a bed capacity of 29,446, furnished estimates of the replacement value of the buildings and grounds of their places.

In general, studying the cost of sanatoria and the tuberculosis hospitals, it is noticed that the buildings are valued, on an average, at ten times the ground. The 177 institutions replying stated that their places had cost in all $110,745,079, which would indicate, for the entire group of 73,715 beds in the United States, a total amount of $277,000,000 as the value of the sanatoria and hospitals now set aside for tuberculosis. The cost of establishing a tuberculosis bed in the United States averages, therefore, $3,761.

Building an institution is, of course, only the first step; each day, and year after year, it has to be maintained. The institutions furnishing information on the cost of operation numbered 198, and represented 32,073 beds. Their maintenance cost during the last calendar or fiscal year was $36,096,025, or an average, on the basis of beds in use, of $1,125 per patient a year, $21.60 a week. For the entire United States, from this figure, we see that there is required for the maintenance of tuberculosis sanatoria and hospitals nearly $83,000,000 annually.

The range of the weekly cost of maintenance varies greatly throughout the country, presumably also with the type of care given patients. In New York State the weekly maintenance is anywhere from ten to thirty-nine dollars; in Massachusetts up to thirty-three dollars a week; in Maryland between eleven and nineteen dollars a week; in California between fifteen and forty-one dollars a week; in Colorado up to forty dollars; and in New Jersey between sixteen and twenty-eight dollars a week. The cost is usually lower in the South.

The highest maintenance cost, on the other hand, is usually in the Federal institutions, where undoubtedly the equipment is of the latest, and where perhaps more adequate remuneration is given to the staff than is the case in so many other institutions obliged to struggle along as best they can. Too close a comparison of the cost of equipment and of maintenance cannot, of course, be made in such a preliminary survey. Undoubtedly many institutions are better located than others for economical operation, but with such a variation in so important a daily concern the subject should be further investigated, with proper qualifications of the items considered so as to make them comparable. There are elements of food, labor, professional care, technical services, heating, repairs, special activities, depreciation, which all need first to be carefully identified; but the study should repay.

ECONOMIC LOSS FROM TUBERCULOSIS

Dr. Lotka, of the Metropolitan Life Insurance Company, has taken the trouble to make for this survey a tentative estimate of the economic value of the lives now being lost because of tuberculosis in the United States. For males, who are in the majority among tuberculosis deaths, Dr. Lotka figures that the annual loss from the investment and value of the lives taken reaches a billion dollars a year, each life in the age-group represented by tuberculosis victims being worth in America, on an average, $21,600.

This amount makes no allowance at all for the lives of females dying from tuberculosis, as it is not readily feasible to set a monetary value upon the services which generally they render in the home. But, with the coming of women in larger numbers nowadays into employment, the total loss arising from tuberculosis mortality alone in the United States must be even more than one thousand million dollars a year.

LENGTH OF STAY

Among all types of cases discharged—or terminated—from the tuberculosis institutions in the United States last year, the replies received from the institutions reporting permit a classification of the length of stay of almost 96,000 patients, including the 20 per cent who died, from the grand total of 102,680 discharged from all the institutions.

If sanatorium treatment or hospital care is to be effective, it must be given over at least a fair period in so chronic a condition as tuberculosis. The study of the length of stay[6] of patients in institutions reveals at once that in an unfortunately large proportion such an opportunity is not seized. More than 40 per cent of all patients remain in sanatoria or hospitals less than three months. As a matter of fact, last year 16,377, or 17 per cent, of the total patients discharged, remained less than one month; 23,243, or 24 per cent, from one to three months; 20,774, or 22 per cent, from three to six months; 15,623, or 16 per cent, from six to nine months; and 19,881, or 21 per cent of the total, nine months or more.

[6] The average length of stay of all patients was one hundred and seventy-four days (five months and three weeks), and excluding the 10 per cent exceptional cases, particularly in private sanatoria, staying more than a year, the average stay was one hundred and thirty-one days.

In 5 large hospitals in different parts of the country it was found that 24 per cent of all their patients had remained less than a month, whereas 5 sanatoria had lost only 7 per cent of their patients in the same period. Frankly, the lesson should be understood. Attractive, well-managed, successful sanatoria are preferred.

The length of stay of patients varies, however, greatly even among sanatoria. For instance, those of Pennsylvania and New Jersey retain 89 or 90 per cent of all their patients more than one month; but, in the reporting institutions of North Carolina and Tennessee, from 23 to 25 per cent of their patients leave in less than thirty days. In the Minnesota institutions 90 per cent of the patients are retained more than a month. A certain municipal sanatorium, where there is a record of insufficient personnel and of overworking patients, loses one out of every five admitted within thirty days, though all the patients sent there are in need of treatment.

Business plants consider unnecessary turnover as a wastage on the investment. Why should not the same attitude be taken in the management of institutions which frequently represent great sums of public money and which deal in human lives? Why accept any lower standard here than that for common business projects?

Are tuberculosis institutions to be only for educational training, or are they to be for curative treatment? If they are only for the first purpose, let them be frankly organized for intensive training in hygiene and correct living. But if they are, as most patients really want them to be, for the recovery of lives threatened, then let such as have an undue proportion of loss of their honest prospects seriously question and reform their methods. For the great investment in tuberculosis institutions at present, and for the large number of patients in need of treatment, there is in many sanatoria an unduly large loss of opportunity, and it would frankly be better to have fewer wasteful short-term admissions and more real work with patients who stay.

TYPES OF CASES

In the survey of tuberculosis hospitals in the United States the institutions were asked for a classification of the types of cases among those terminated during the last fiscal or calendar year.

It is first evident from the replies of 206 institutions, with 37,000 beds, that there are now being disposed of in the entire country some

102,000 cases annually (including cases that died, and which are 20 per cent of the total); and, as in a large group of institutions the discharges must equal in the long run the admissions, we may likewise state that slightly more than 100,000 patients are admitted each year to tuberculosis sanatoria and hospitals in the United States.

Of the 102,680 cases of all types discharged "last year" from sanatoria and hospitals, detailed replies to the question of how many were diagnosed tuberculous, nontuberculous or doubtful, indicate that in 1925 in all the institutions in the United States 89,310, or 88 per cent, were recognized as tuberculous. Eleven per cent, or 11,890, were returned as nontuberculous, and 1 per cent, or 1,480, as doubtful cases.

On the question of how many of their tuberculosis cases were pulmonary or nonpulmonary, the figures in the replies indicated, in a total of 91,319 tuberculosis cases, 86,019, or 95 per cent, as being of the pulmonary type, and 5,300, or 5 per cent, as suffering from nonpulmonary forms of tuberculosis. The latter figure shows the somewhat low proportion of surgical and other forms of tuberculosis than pulmonary in the United States, though in a measure the figures would probably be raised were there more institutions for the care of children. The demand, however, cannot be very great, considering the returns for this last group.

The stage of the disease among pulmonary cases was ascertained for the patients discharged last year in 176 institutions with 29,742 beds. This classification is all important when one considers what should, if possible, be the equipment and the staff available in the sanatoria. For a total of 85,960 pulmonary cases terminated last year in all the sanatoria and hospitals in the United States, the returns from the institutions reporting would indicate 13,800 patients classified as incipient, or only 16 per cent of the total; 28,900, or 34 per cent, moderately advanced; and 43,260, or 50 per cent, far advanced. It is, therefore, obvious that at present one-half of all the cases sent to sanatoria and hospitals are far advanced, and we have at once an indication of the much greater proportion of infirmary beds needed than is usually available. Further, this would indicate the all too lamentably low proportion of early cases now reaching institutional care.

With better selection, or rather better case-finding and social-service work, undoubtedly twice as many recoveries could be secured, as well as lives saved, were treatment more timely. It is obvious, too, that at present the bulk of tuberculosis institutional work is directed toward

advanced cases rather than toward early or favorable cases. The data should also dispose at once of the thought that at present sanatoria can be reserved for incipient cases. As a matter of fact, the bulk of sanatorium cases, even in places which select highly, are already in the second stage of the disease when first received.

RESULTS OF TREATMENT

With only 16 per cent of the cases of tuberculosis in institutions coming when still in the incipient stage, it can be better appreciated how difficult it is to arrest the disease of the advanced cases received, and we may well marvel at what is still being accomplished against these odds. One hundred and eighty-four institutions, with 31,581 beds, reported for last year the comparative discharge condition of their tuberculosis cases, both the pulmonary and the few nonpulmonary cases. The ratios of their results applied to the total beds in the United States indicate, in a total of 89,368 tuberculosis histories closed last year, that 17,984 patients, or 20 per cent, had died while in the institutions. This figure shows us at the same time that approximately 19 or 20 per cent of all tuberculosis deaths in the United States now take place in institutions; in New York City it is as high as 40 per cent. Second, 20,740, or 23 per cent, of the patients in sanatoria and hospitals, left with condition unimproved or progressive. Third, 37,704 patients, or 42 per cent of the total, left with condition either improved or quiescent; and a great many of these, with the health-training acquired and their resistance raised, were placed on the road to an ultimate recovery. Finally, 12,940 patients, or 15 per cent of the total, were reported as having their disease apparently arrested before returning home.

The percentages of results naturally vary in certain institutions and, of course, are largely dependent upon the stage of the disease of the patients when they first enter.

The subject of the results of treatment would need much more than this preliminary investigation to permit a fair appraisal of findings and differences. One impression, however, does remain clearly in the mind of the investigator after studying the replies of the institutions; namely, that in many places the medical authorities had no idea whatever whether or not they were attaining the success possible in the majority of cases or in only half of them. There are undoubtedly institutions where the after-mortality of the patients is twice that of other institutions. The

plain truth is that in many a community patients treated at public expenditure are not being given an equal chance for their lives. More studies of the ultimate results, rather than of the always debatable immediate results, should be made with proper qualification of the types of patients compared, with careful allowances for factors known to influence death-rates, such as age, sex, extent of disease, severity, presence or absence of bacilli, and the findings compared with up-to-date life tables of the general normal population as the common standard.[7] But that presupposes the careful tracing of patients from institutions, a labor which has been assumed at present by only a few. There would, however, be less occasion for statements of the failure of the sanatorium movement were such standards applied to what amounts at present to practically unmeasured medical work in this enormous undertaking of the institutional treatment of 100,000 tuberculous a year, with all its possibilities for the loss or the saving of lives.

FOLLOW-UP AND AFTER-CARE

An attempt was made in this survey to ascertain the facts available on the question much discussed, at least by sanatorium executives, of follow-up work and after-care.

A large majority of the sanatoria replied that they had no plans whatever for follow-up and after-care of their patients. A few felt that they had made a beginning, however, by attempting to trace their patients. For this purpose they usually sent out a report form requesting former patients to tell them something of their condition; but, beyond merely ascertaining whether they are alive or dead, little more is done. Two or three institutions attempt to arrange an annual homecoming function, and notify such as wish or are able to come to do so. The effort of the sanatoria to ascertain how many of their former patients are still alive is rarely designed to give them any further assistance, but it does frequently give the medical authorities of the institution an opportunity to check the results of various forms of special treatment, and the clerical work involved in this tracing should prove to be well worth while if the findings are properly studied.

[7] For method, see Elderton and Perry, *A Fourth Study of the Statistics of Pulmonary Tuberculosis: the Mortality of the Tuberculous, Drapers' Company Research Memoirs*, Dulau & Co., London, 1913. Also, *Pulmonary Tuberculosis: Mortality after Sanatorium Treatment*, by Bardswell and Thompson, Medical Research Committee, National Health Insurance, London, 1919.

All the institutions under the direction of the United States Veterans' Bureau replied that there was provision, after discharge, for the continued observation of their patients through the various regional offices.

Two or three tuberculosis institutions had established a *liaison* with local tuberculosis associations.

The smaller proportion of sanatoria which did have arrangements for follow-up and after-care of their patients usually accomplished this by two methods: *First*, through county tuberculosis or public-health nurses, where the patients reside, or through arrangements with local visiting nurses' associations. *Second*, particularly in the larger centres of population, through reporting their discharged cases to the city health authorities, where frequently there is already a system of sanitary supervision through clinics, dispensaries, and home visiting.

As to the efficacy of the follow-up work through county tuberculosis or public-health nurses and visiting services, the sanatorium authorities occasionally remarked that the system is not efficient or satisfactory. Three or four institutions actually employ one or two field nurses to follow up their own cases. In a few sections perhaps the most satisfactory arrangement is where the same tuberculosis authority and staff conduct both the clinic work in the towns or communities and the sanatorium or hospital.

In certain States in the East a more consistent attempt is made to connect the sanatorium with existing follow-up systems. In New York State, 31 institutions among 38 studied reported such arrangements, most of them being with the county tuberculosis or public-health nurses in the more rural sections and through the tuberculosis division of the Department of Health of New York City. In Pennsylvania the state and municipal dispensary systems are utilized by the public institutions, except by one or two smaller private sanatoria. In Chicago the Municipal Sanitarium operates its own dispensaries and patients are seen at the clinics and in their homes,—in fact, are followed, as the report stated, until the disease of the patient is arrested or till death. A similar system is attempted in Massachusetts, by the State sanatoria, to follow patients through the general office of the Massachusetts State Sanatoria.

But in the greater number of places in the United States the follow-up of discharged sanatorium cases and their after-care is either nonexistent or inadequate, except perhaps in a few large cities where there already is organized sanitary supervision of "at home" cases of tuberculosis.

We personally doubt that it will ever be possible to really direct after-care of former sanatorium patients from the sanatoria themselves. It would neither be practical nor wise.

Let us recall that almost 100,000 patients are now discharged from the institutions, returning to their homes, scattered all over the country. Certainly no adequate staff, with the distances to be covered and the calls to be repeated, can be organized from out-of-the-way posts, as the sanatoria often are, nor are the sanatorium authorities usually familiar firsthand with conditions in the towns and cities. As a matter of fact, no one is more isolated from the ordinary currents of daily life than the sanatorium executive who has settled in an institution.

Secondly, follow-up and after-care in the homes of patients who have been in institutions constitute only a fraction of the work to be done with "at home" cases of tuberculosis, who have not yet been in a sanatorium nor ever will be in one and yet are registered in the various communities. For the 12,000 patients in New York City who go through institutions each year, there are 28,000 in their homes, and those who went to institutions probably scattered themselves not only in the public institutions nearby, but also in many health resorts throughout the country.

In our opinion, sanatorium authorities have their hands full within their own walls to bring up and maintain the standards of sanatorium care given in certain first-class institutions. The care of the patient at home, whether before going to an institution or after returning, and for those who will always remain at home, must be demanded instead from the various local tuberculosis authorities. We may even add that there would be much less necessity for talk of after-care, of relapses, and of the failure of sanatorium treatment, were institutions first to complete their task with the sick while they have them under their observation. In many sanatoria patients are kept too short a time, and in certain institutions medical care is inadequate.

It is the experience of social workers in the cities that with patients from a few select institutions they have not a fraction of the problems they have with those from other institutions, because the patients in the first places have been made fit to resume their occupations, and have been properly educated concerning how to take care of themselves as well.

TABLE 6

*Tuberculosis hospitalization and mortality in various countries**

COUNTRY	POPULATION		TUBERCULOSIS† MORTALITY			HOSPITAL AND SANATORIUM BEDS (c)	BEDS AVAILABLE FOR EACH TEN DEATHS
	Inhabitants (a)	Year	Deaths (b)	Year	Rate per 100,000		
New Zealand	1,431,079	(1924)	736	(1924)	51	658	9
Canada	9,215,000	(1924)	7,675	(1924)	83	5,238	7
United States	112,078,611	(1924)	99,579	(1924)	89	73,715	7
England and Wales	38,746,000	(1924)	41,103	(1924)	106	20,750	5
Netherlands	7,358,368	(1925)	7,263	(1925)	99	3,000	4
Germany	62,365,478	(1925)	83,000	(1925)	133	35,000	4
France	39,209,518	(1921)	66,824	(1920)	170	29,171	3 to 4
Italy	40,116,700	(1924)	65,000	....	162	7,000	1
Czechoslovakia	13,982,726	(1921)	40,000	(1924)	250	5,291	1
Japan	59,736,704	(1925)	120,719	(1921)	213	3,000	‡

* Compiled by G. J. Drolet, Research Service, New York Tuberculosis and Health Association.

† All forms of tuberculosis.

‡ In Japan only one tuberculosis bed available for each forty deaths from that disease.

Notes: Sources of Information:

New Zealand: (b) *Report, Health Organisation, League of Nations, Statistics of Notifiable Diseases for 1925*, p. 116; (a) (c) *1926 New Zealand Official Year Book*, pp. 175, 205. Figures of beds are based, first, on actual patient census in 6 public institutions reported upon for December 31, 1925, and, second, on an estimate of 50 beds in each of 5 other private sanatoria.

Canada: (a) (b) (c) *Bulletin, International Union against Tuberculosis*, July, 1926, p. 95.

United States: (a) Population estimate for continental United States based on Federal Census. (b) Total tuberculosis deaths in entire country from reports, first, in the Registration Area and, second, to the United States Public Health Service from local registrars in remaining sections. (c) *1926 Directory, National Tuberculosis Association.*

England and Wales: *1924 Report, Chief Medical Officer, Ministry of Health.*

Netherlands: (a) (b) *Bull. Int'l Union against Tub.*, July, 1926, p. 100. (c) The total beds, public and private, are estimated on basis of 1,655 reported for public institutions alone.

Germany: (a) *1925 Report, Health Organisation, League of Nations.* (b) In 1923, when there was a marked recrudescence of tuberculosis in Germany, a total of 93,074 deaths were reported (*Statistiche Jahrbuch*). In 1925 the reports to the Health Section of the League of Nations from 46 cities, with a total population of 16,746,000, indicated a drop to 19,805 tuberculosis deaths from the record of 29,432 in 1923. The 1925 estimate for Germany is obtained by deducting from the 1923 total the ten thousand lives gained in the large cities. (c) Tuberculosis beds according to *Difesa Sociale*, quoted, *Bulletin, N. Y. Tub. Ass'n*, May–June, 1924. The actual beds available in Germany were, however, reduced after the war owing to the financial difficulties of maintaining them all.

France: (a) (b) (c) *1924 Report, Statistique Générale de France*, and *Bull. Int'l Union against Tub.*, July, 1926. In the grand total of 29,171 tuberculosis beds in general hospitals, as well as in special institutions, more than 12,500 are reserved for the care of surgical cases, mostly children, leaving a greatly reduced number for the more dangerous pulmonary cases. Bruno, in 1923, figured for France only 9,960 beds for pulmonary cases, and Guinard but 7,200.

Italy: (b) (c) According to Campani in a report of the Italian National Federation against Tuberculosis, only 7,000 beds, mostly in the North, are reserved for tuberculosis. (*Bull. Int'l Union against Tub.*, July, 1926.)

Czechoslovakia: (b) Estimate of 40,000 tuberculosis beds is based on the figures assembled for a series of years in the different sections of that country in Hůlka's *Survey* of 1922; (c) beds, same source.

Japan: Report, Satow, Medical Officer of Health, Japanese Department of Home Affairs, *Bull. Int'l Union against Tub.*, July, 1926.

TUBERCULOSIS HOSPITALIZATION AND THE TUBERCULOSIS DEATH-RATE

To gauge, if possible, the influence of tuberculosis hospitalization upon the general tuberculosis death-rate, the writer has gathered the latest available reports from ten countries in different parts of the world, both as to the total number of beds available and the mortality from all forms of tuberculosis. Besides the United States these include Germany, Italy, France, England and Wales, the Netherlands, Czechoslovakia, Canada, New Zealand and Japan. The total population concerned is no less than 384,240,000; and, within a single year, in these ten countries, 531,899 deaths from tuberculosis were reported. For the organized institutional care of tuberculosis patients there are reported to be 182,823 beds available in these countries. The details for each section may be studied in table 6.

Before going on to an analysis of the relative conditions revealed by this broad survey and particularly the question of ascertaining the possible relation between the tuberculosis death-rate prevailing in each country and the available resources for the care of the sick, let us consider for a moment the tremendous influence of tuberculosis in the sections of the world noted here.

First, the variations in the tuberculosis death-rate: In New Zealand, for instance, a rate of 51 deaths per 100,000 population as against a death-rate of 213 in Japan. For every life taken by tuberculosis in New Zealand four is the toll paid in Japan.

Second, the loss in a single year of 531,899 lives.

Third, the cost of building institutions to provide 182,823 beds and of maintaining them each day throughout the year.

Finally, a closer study of the relationship of tuberculosis mortality and of the institutional facilities for its control in each country brings out striking facts, we believe, which indicate *how important the factor of hospitalization must be.*

In New Zealand, in a population of a million and a half, 736 tuberculosis deaths were reported in 1924. And, as there are 658 hospital and sanatorium beds available, we see in that country practically nine tuberculosis beds available for each ten deaths. Furthermore, as MacEachern, who recently investigated the remarkable hospitals in that country on the invitation of the local branch of the British Medical Association, said, "Financial support is guaranteed by the Government, assuring hospitalization for even the poorest citizen of the Dominion." In New Zealand, where is to be found the highest ratio of beds available for each death, we have the lowest tuberculosis death-rate, 51 per 100,000.

In 1924 in New Zealand, 372 tuberculosis deaths, or more than 50 per cent of all such deaths in the entire country, took place in hospitals.

In Canada, the 1924 reports show 7,675 tuberculosis deaths in the population of nine million, and a mortality rate of 83. The latest figures for that country, mentioned in the *Bulletin of the International Union against Tuberculosis*, showed 5,238 hospital and sanatorium beds available and, therefore, a ratio of seven beds for each ten tuberculosis deaths.

In the United States, among one hundred and twelve million people, the combined *Reports* of the Bureau of the Census and of the United States Public Health Service showed in 1924 a total tuberculosis mortality of 99,579, or a death-rate of 89 per 100,000. And, as there are now known to be 73,715 beds available, we have a ratio here of seven beds to each ten deaths. The United States, with 29 per cent of the population considered in this world-wide survey, has 40 per cent of the total facilities disclosed in the ten countries.

In England and Wales, with a population of thirty-nine million, there were noted 41,103 tuberculosis deaths in 1924, and the mortality rate from this cause was 106. As the reports of the Ministry of Health showed the total number of tuberculosis beds available to be 20,750 in that year, we have in England a ratio of five beds available for each ten tuberculosis deaths.

In the Netherlands, among 7,350,000 people there were 7,263 tuberculosis deaths in 1925 and the death-rate was 99 per 100,000. The 3,000 tuberculosis beds reported available indicate a ratio of four for each ten deaths.

Germany, with a population of more than sixty-two million people, suffers an annual tuberculosis mortality of approximately 83,000, indicating a tuberculosis death rate of 133 per 100,000; and for the 35,000 beds available we see a ratio of four for each ten deaths.

For France, with thirty-nine million people and with practically stationary numbers for both population and mortality, the latest report showed 66,824 tuberculosis deaths, and the nowadays high rate of 170 still prevailing there. Some 29,030 tuberculosis beds have lately been credited to that country, but, as an unusual proportion of them is devoted to surgical cases of tuberculosis, mostly in children, Bruno figures 18,000 beds for France, of which only 9,960 are available for the more dangerous pulmonary cases. In France, therefore, it is probable that the larger number of beds said to be available has come into use only very recently, and the actual ratio is perhaps less than four for each ten deaths.

Italy, with more than forty million people, still has an annual tuberculosis mortality of 65,000, says Campani in his recent survey for the Italian National Federation against Tuberculosis, which would show a tuberculosis death-rate of 162. And, as there are only some 7,000 beds available,—practically all in the northern section,—a ratio of only one bed to each ten tuberculosis deaths is noted in Italy.

In Czechoslovakia, among the fourteen million people in the various sections which now form that country, the reports of Hůlka indicate an annual mortality of 40,000,—said to have been even rising in some agricultural sections that have lately become industrial; and a death-rate of higher than 250 is found. The 5,291 tuberculosis beds available in Czechoslovakia show a ratio of little over one bed for each ten deaths.

Japan, with sixty million people, has a tuberculosis mortality, says Satow, the Medical Officer of the Department of Home Affairs, of 120,000 annually, or a death rate of 213. And as the tuberculosis beds available, public and private, amount to only 3,000 we find a ratio of less than one bed available for each forty deaths in Japan.

CONCLUSIONS

1. There is, therefore, a striking correlation to be noted in these figures between the tuberculosis death-rate and the ratio of beds available. Taking the three countries with the lowest rates, below 100 per 100,000 population, namely, New Zealand, Canada and the United States, we notice there the highest ratio of beds available,—from seven to nine for each ten deaths.

2. In the intermediate group, in the order of their tuberculosis death-

rate, the Netherlands, England and Wales, and Germany, we find the ratio of beds available is four or five for each ten deaths.

3. In the nations with high tuberculosis death-rates, Italy, France, Japan and Czechoslovakia, we find instead a diminishing or low ratio of beds available for the control of tuberculosis.

4. Of course, the writer does not believe that tuberculosis hospitalization is the only factor controlling the tuberculosis death-rate. On the contrary, he feels that with it two other outstanding factors play a very great part: *first*, the factor of general living and working conditions; and, *second*, that of racial resistance (which he believes is a condition acquired mainly through contact with tuberculous infection, and in proportion perhaps to its frequency and duration either in an individual or his ancestors; in other words, previous tuberculization of the race or the group, the effects of which are transmissible).

5. But, along with the influence of living and working conditions, and of previous tuberculization, we must acknowledge that tuberculosis hospitalization would seem to be one of the outstanding factors throughout the world in the control of the White Plague.

FOLLOW-UP INFORMATION ON 1,747 TUBERCULOSIS PATIENTS ONE TO SEVEN YEARS AFTER DISCHARGE FROM A SANATORIUM

R. G. FERGUSON[1]

The Saskatchewan Anti-Tuberculosis League, operating sanatoria at Fort Qu'Appelle and Saskatoon, has made a consistent endeavor for several years to keep in touch with the patients discharged from its sanatoria, not alone that it might give them advice but also that it might gain information which would be of value to future patients. For practical reasons, and in view of the fact that assured recovery from tuberculosis cannot be accomplished in less than from two to four years, the cure begun at a sanatorium must be continued under home conditions. It was thought that, by a careful study of the recoveries, relapses and deaths of those previously treated, information could be gleaned which would prove to be of the utmost benefit to those suffering from tuberculosis, inasmuch as the latter, knowing something of the experience of others, would be better able to cope with their own problems of occupation and environment.

Accordingly, a study has been made of the 1,747 tuberculosis patients who returned home after receiving treatment at the Fort Qu'Appelle Sanatorium between October 10, 1917, and December 31, 1924.

FACTORS TO BE CONSIDERED

In representing the more permanent results of treatment many factors must be considered in order that the conclusions recorded may be compared with those of other workers.

First, one must have some idea of the racial immunity of the people who have been treated. Studies carried on in different parts of the world have shown that there is considerable difference among various races in their resistance to tuberculosis. One must also have some idea of the patients' stage of disease on admission, the proportion which were nonpulmonary and the proportion of those of acute or chronic type.

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Again, the duration of treatment and stage of improvement or arrest on discharge are of great importance. Furthermore, the ages of the patients treated are of considerable importance. It would be entirely misleading to compare results in persons who have broken down in the regenerative period of life with those in the degenerative period. Again, the occupation, living conditions and environment, to which the patients return in a rural district, cannot be compared with those to which they would return in an urban district.

Finally, there are the physiological burdens of child-bearing and accidental crises, such as emergency surgical operations and acute epidemic disease, the extent of which must be known in any group of patients studied.

CLASS OF PATIENTS

Since accommodations were very limited during the first fifteen months of the operation of the sanatorium, there was some selection of patients, with the idea of eliminating those with bad prognoses. During the succeeding five years all classes were admitted, so that the group followed is representative of the active cases in Saskatchewan that are actually breaking down with tuberculosis and, for the most part, cases of the more severe type which are unsuitable for home treatment. The prognosis of patients on admission is difficult to determine in retrospect without prejudice, and perhaps a fairer indication of the number of cases hopeless on admission can be obtained from the fact that nearly 2 per cent died within a month of admission and 10.49 per cent died in the sanatorium during their first period of treatment.

The 1,747 patients followed up is, to some extent, a selective group, inasmuch as those with the poorest prognosis were eliminated by death in the sanatorium. A study of those discharged brought out that 5.72 per cent were nonpulmonary. Of the pulmonary cases, 23.29 per cent were incipient, 33.58 per cent moderately advanced, and 37.42 per cent far advanced.

Further information may be gathered regarding the classes of patients treated by a study of the amount of improvement achieved while under treatment at the sanatorium, which shows that of the 1,747 followed 15.91 per cent were discharged apparently arrested or better, 27.36 per cent quiescent, 34.11 per cent improved, and 22.66 per cent unimproved.

LENGTH OF TREATMENT

The length of stay in the sanatorium, other things being equal, was found to bear a very direct relation to the permanence of results obtained. This we consider due not only to the better condition of the patient on discharge but also to the more adequate education and experience which the patient secured by remaining for a longer time. The length of stay has increased from year to year, as shown by table 1, the average for the 1,747 being six and a half months:

TABLE 1

	MONTHS		MONTHS
In 1918	3.18	1922	8.30
1919	3.57	1923	7.90
1920	6.05	1924	9.20
1921	7.40		

TABLE 2

Age, sex and marital state of 1,747 active tuberculosis patients

AGE	TOTAL	PER CENT	MALE	MARRIED	SINGLE	FEMALE	MARRIED	SINGLE
years								
Under 5	19	1.08	9		9	10		10
5 to 9	68	3.89	26		26	42		42
10 to 14	108	6.23	50		50	58		58
15 to 19	220	12.58	108		108	112	14	98
20 to 24	368	21.06	210	24	186	158	63	95
25 to 29	340	19.46	212	76	136	128	86	42
30 to 34	235	13.04	149	86	63	87	71	16
35 to 39	194	11.10	126	87	39	68	64	4
40 to 44	104	5.96	69	46	23	35	31	4
45 to 49	43	2.51	28	23	5	15	15	
50 to 59	38	2.17	25	22	3	13	11	2
60 to 69	9	0.51	6	6		3	3	
	1,747		1,018	370	648	729	358	371

The considerable increase in the period of treatment resulted, as will be seen later, in a corresponding betterment in permanent condition.

AGE GROUPS

Table 2 shows that, as far as Fort Qu'Appelle Sanatorium is concerned, 77.24 per cent of those patients who returned home were in age-groups

between 15 and 40, while 11.20 per cent were under 15, and 11.15 per cent over 40.

The small percentage of children shown is not due to the absence of juvenile tuberculosis in Saskatchewan, but is partly owing to the fact that no accommodation was available for children during the first two and a half years of the operation of the sanatorium, and, second, to the fact that during the period following the war there was an excess of young adult males who were war casualities, which enlarged the number in that group. The small percentage of our patients over forty is noteworthy, and is consistent with the curve of the death-rate in Saskatchewan, which shows only a small percentage of tuberculosis deaths after middle life. This has been explained by authorities as due to the rarity of breakdowns after middle life in agricultural communities, although such breakdowns are common in industrialized communities. No doubt it is also partially due to the fact that, owing to recent colonization, less than the average proportion of the population is in the age-group over forty.

RACIAL IMMUNITY

Racial origin is a factor which has some bearing upon immunity, and consequently upon more permanent results in the treatment of tuberculosis. The susceptibility of primitive peoples is well known to all who are interested in tuberculosis, as is also the marked resistance to the disease that has been attained by the Jewish race.

As far as our patients are concerned the extremes of resistance or susceptibility have little effect on the general resistance, as only 0.66 per cent are Hebrews, while 2.25 per cent are full-blooded Indians and 1.02 per cent half-breeds. The greater part of our patients, nearly 70 per cent, have their racial origin from people in the British Isles, and 27 per cent are recent descendants of peoples of Central Europe, and are presumably, therefore, relatively highly immunized.

OCCUPATIONS OF PATIENTS FOLLOWING DISCHARGE

A study of the occupations followed after discharge of those who were able to go back to work shows that a large number, 755 out of 952, or 79 per cent, returned to their previous occupations. Twenty per cent changed their occupations. This change has usually been from an outdoor, heavier occupation to one that is indoors and lighter. As

far as this group is concerned, it would appear that if a patient is in a good enough physical condition to undertake work he will do pretty well by returning to his previous occupation. Nevertheless, the light indoor occupations have proved most suitable. A study of the relapses, which is to follow, will throw further light on this important subject.

TABLE 3

Occupations of 952 persons who are now able to work

Farmers	119	Postmasters and clerks	6
Housewives	220	Policemen	4
Farm laborers	42	Stenographers	9
Laborers of many varieties	76	Telephone operators	3
Storekeepers and clerks	43	Nurses, graduate	10
Office clerks	47	Nurses, in training	2
School children	94	Hospital attendants	2
Students	23	Clergymen	5
Chorers	48	Nun	1
Teachers	17	Trapper	1
Printer	1	Contractors	2
Travelling salesmen	17	Physicians, veterinary surgeons, etc.	3
Houseworkers, including domestics and those remaining at home	60	Lawyers	2
Dressmakers, milliners, etc	4	Waiters	2
Tailors	1	Painters	5
Cooks	2	Agents	5
Mechanics, heavy work	13	Laundry workers	2
Mechanics, light work	8	Accountants, including town clerks and municipal secretaries	12
Carpenters	9	Business managers	7
Shoemakers	1	Gardeners	3
Barbers	3	Messengers	3
Miners	2	Telegraphers	2
Light technical workers	3	Editors	1
Bricklayers	2	Unknown	6

ECONOMIC AND SOCIAL FACTORS

The economic condition of the group studied, as far as the 514 ex-soldiers are concerned, is relatively good, since they were discharged for the most part on full pension of $75.00 per month for single men with an additional allowance for dependents in the case of married men. An idea of the condition of the remaining 1,234 may be inferred from the fact that 80 per cent were indigent at the time of admission to the sanatorium. Taken altogether, about 4 out of 10 are in fair circumstances, while 6 out of 10 are in poor circumstances.

The patients treated here are representative of the social and occupational groups in an agricultural Province. In this respect this group is widely different from others available for comparison, as the latter deal with patients drawn almost entirely from industrial communities.

STUDY OF RELAPSES

One of the outstanding facts about tuberculosis is the tendency of the disease to relapse. A relapse has been interpreted as a second breakdown, giving rise to symptoms requiring further treatment. The better the condition on discharge the less the tendency to relapse, but relapses did occur in cases in which the disease was apparently arrested and even apparently cured. Usually there was an outside cause discoverable in the living or working conditions of the individual, accounting, in part at least, for the second breakdown, but occasionally no such cause could be found.

Of the 1,747 patients who returned home 190, or 10.87 per cent, relapsed. The percentages of relapses during the first three years of operation of the Sanatorium were very much higher than in subsequent years. About 1920, when the period of sanatorium treatment was noticeably prolonged, there was a definite drop in the percentage of relapses, which has since been maintained. In other words, it would appear that when insufficient treatment has been given the length of treatment bears an inverse relationship to the percentage of relapses.

A study of the cause of relapse in the group of patients which have come under our observation was made in order to ascertain to what extent they might be prevented. The classification in table 4 is based on occupational and environmental factors, together with other incidental causes, such as intercurrent disease, pregnancy and surgical operations.

From table 4 it will be seen that insufficient treatment originally holds first place, accounting for 27.89 per cent of the relapses. This cause is being remedied as better financial provision is made for those unable to pay. Overwork takes second place as a cause of reactivation, accounting for 22.10 per cent. This cause could be reduced if part-time or lighter employment could be secured for the initial period. The third largest group is that of patients who broke down, without any apparent reason, as everything appeared to be favorable. These patients are classified under *Unexplainable Relapses*, and constitute 12.57 per cent. Intercurrent disease is also a major cause, accounting for 9.53 per cent of the

relapses. This cause will subside with improvement in general health and further control of infectious diseases. Another important cause is unhygienic living conditions, accounting for 7.63 per cent.

A noteworthy fact regarding the group which we have studied is that no cases of relapse were reported as being caused by pregnancy. In two cases, however, abortion occurred, and although it was not the primary cause of relapse it was probably a contributory cause. Our follow-up reports show that 67 children were born to 51 of the women who received treatment. As a special question was not asked regarding children born after discharge, except in the cases of relapse, such children as were reported were only incidentally mentioned and the number, therefore, cannot be considered complete.

TABLE 4

Causes of relapse

CAUSE	NUMBER	PER CENT
1. Insufficient treatment originally	53	27.89
2. Intercurrent disease	18	9.53
3. Concurrent disease	7	3.68
4. Overwork	42	22.10
5. Unhygienic living conditions	18	9.47
6. Unhygienic working conditions	1	0.52
7. Indiscretion (whether in recreation or morals)	14	7.36
8. Unexplainable	24	12.57
9. Pregnancy		
10. Operative procedure	4	2.10
11. Not known	9	4.73
	190	

OCCUPATION IN RELATION TO RELAPSE

A study of occupation in relation to relapse shows that in the case of 407 females who were engaged in indoor occupations 43, or 10.06 per cent, relapsed. In the case of 205 males who were engaged in indoor occupations 39, or 19.02 per cent, relapsed. In the case of 334 males who were engaged in outdoor occupations 94, or 28.01 per cent, relapsed. When we consider the males alone we see that there is a marked increase in the relapses among those engaged in outdoor occupations. This is not because they were working outdoors, but because outdoor occupations in an agricultural Province represent farming and other labor, which are heavy occupations. The majority of those who broke down

due to overwork were patients undertaking outdoor work. This cause of relapse could be considerably reduced if graduated physical labor under supervision could be provided for those who return to farming and other heavy work.

A study was also made of relapses in relation to condition of patients on admission (table 5).

From this study it was found that the larger number of relapses occurred among patients in the incipient and the moderately advanced stages, and that the percentage of relapses among the clinical cases was larger than among the bacillary cases.

TABLE 5

Relapses in relation to condition on admission

CLASSIFICATION	NUMBER RELAPSED	PERCENTAGE OF 190
Clinical I	35	18.42
Clinical II	64	33.68
Clinical III	25	13.15
Bacillary I	4	2.10
Bacillary II	28	14.73
Bacillary III	24	12.63
Nonpulmonary	10	5.26
	190	

It must be taken into consideration that many of the advanced cases became progressively worse, and never recovered sufficiently to relapse. Among these are found not the relapses but the deaths. In the second place, the patients who had germs in their sputum realized to a greater extent the need of treatment and, as a result, coöperated better. Finally, the larger number of relapses among the clinical cases is to some extent due to their having improved quickly after admission and having returned home too soon. Unlike the bacillary cases they did not take the necessary precautions after dicharge, and relapse was the inevitable result.

Even after relapse, the early cases returned to the sanatorium in better condition than the majority of patients, and the results of their second periods of treatment were better than the average results obtained by all classes.

A study was made of the sex and age in relation to relapse, and it was found that of the 1,018 males who returned home 147, or 14.44 per cent,

relapsed. Of the 729 females 4.52 per cent relapsed. In this group the percentage of relapses among the males was considerably greater than among the females. This is probably due to the fact that as far as the single women are concerned their occupation and living conditions were more sheltered than in the case of the males.

TABLE 6

Time since discharge in relation to relapse

TIME	NUMBER RELAPSED	PER CENT
years		
Less than 1	101	53.15
1 to 2	43	22.63
2 to 3	24	12.63
3 to 4	11	5.78
4 to 5	9	4.73
5 to 6	1	0.52
6 to 7	1	0.52
	190	

TABLE 7

Follow-up results year by year after an average period of four years from discharge

YEAR DISCHARGED	TOTAL DISCHARGED ALIVE	WELL AND WORKING		SYMPTOMS AND LIGHT WORK		UNABLE TO WORK		DIED		UNHEARD OF		DIED IN SANATORIUM	GRAND TOTAL OF DISCHARGES
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent		
1918	126	64	50.78	16	12.69	11	8.73	32	25.39	3	2.30	6	132
1919	295	140	47.71	30	10.17	39	13.22	74	25.08	12	4.07	32	327
1920	362	147	40.60	43	11.87	45	12.43	108	29.55	19	5.24	35	397
1921	294	137	46.59	28	9.52	49	16.65	68	23.11	12	4.08	26	320
1922	244	111	45.49	25	12.20	41	16.76	52	21.31	15	6.18	28	272
1923	230	99	43.04	23	10.00	64	27.82	43	18.69	1	0.43	35	265
1924	196	64	32.65	25	12.76	64	32.65	34	17.39	9	4.59	44	240
	1,747	762	43.61	190	10.87	313	17.91	411	23.52	71	4.06	206	1,953

From the standpoint of prognosis, as affected by relapse, time as a factor of safety appears to be of utmost importance. This fact should be kept in mind by all engaged in the treatment of tuberculosis. Consequently a study of time in relation to relapse was made (table 6).

Table 6 shows that almost 90 per cent of the relapses among our ex-patients occurred within the first three years following discharge, and more than half of these occurred during the first year. After the fifth

TABLE 8

Follow-up results after an average period of four years since discharge

YEAR OF DISCHARGE	TOTAL NUMBER DISCHARGED ALIVE	APPARENTLY CURED		ARRESTED		APPARENTLY ARRESTED		QUIESCENT		IMPROVED		UNIMPROVED		DIED		UNHEARD OF		NUMBER DIED IN SANATORIUM	GRAND TOTAL OF DISCHARGES
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent		
1918	126	41	32.53	17	13.49	12	9.52	9	7.92	3	2.30	9	7.92	32	25.39	3	2.30	6	132
1919	295	64	21.69	49	16.52	41	13.85	25	8.81	6	2.03	24	8.44	74	25.08	12	4.07	32	327
1920	362	33	9.11	58	16.02	60	16.57	49	13.53	7	1.87	28	7.73	108	29.55	19	5.24	35	397
1921	294	16	5.44	55	18.70	54	18.36	43	14.68	7	2.38	39	13.27	68	23.11	12	4.08	26	320
1922	244	6	2.45	13	5.32	60	24.59	66	27.04	3	1.23	29	11.88	52	21.31	15	6.18	28	272
1923	230	3	1.34	11	4.78	50	21.73	69	30.00	18	7.82	35	15.21	43	18.69	1	0.43	35	265
1924	196	2	1.02	3	1.53	28	14.28	73	37.24	21	10.71	26	13.26	34	17.39	9	4.59	44	240
	1,747	165	9.44	206	11.21	305	17.41	334	19.11	65	3.72	190	10.87	411	23.52	71	4.06	206	1,953

year the percentage of relapses dropped to 0.5 per cent, which is perhaps not higher than the proportion suffering from active tuberculosis in the total population.

STUDY OF RECOVERIES

As noted in table 7, out of 1,953 tuberculosis patients, 206, or 10.53 per cent, died in the sanatorium prior to discharge. The after-results of sanatorium treatment are shown by a study of the remaining 1,747 tuberculous persons. It is the prognosis of this latter group that is of special interest to tuberculosis workers and to all others who are interested in the expectancy of life of tuberculous persons who have received sanatorium treatment. A report of the present condition, as estimated by our patients themselves as at December 31, 1925, was derived from personal correspondence, and also from questionnaires sent to them inquiring as to their ability to work and the presence of symptoms of disease.

A further study of the present condition of the patients as estimated by medical men was made, the source of information being reports of family doctors, pension-board medical examiners, and sanatorium physicians.

It was thought that by classifying the results secured, both on the basis of the condition as estimated by the patients and that estimated by their physicians, information would be available which could be compared with follow-up reports of other workers based on either source of information.

An analysis of tables 7 and 8 will show that the group *Well and Working*, as estimated by the patients themselves, corresponds more or less with the combined groups *Apparently Cured*, *Arrested*, and *Apparently Arrested*, as classified by the physicians. As was actually found, the *Well and Working* constitute 43.61 per cent of the whole, and the latter combined groups constitute 28.06 per cent. From this it will be seen that some of the patients considered themselves well and working when they were classified by their physicians as *Quiescent*. This over-estimation, due to false convalescence, is a fact which may be frequently observed in actual practice.

STAGES AND RESULTS

From the standpoint of prognosis it will be of interest to all physicians, who are caring for the tuberculous, to know what effect the stage of

disease at the time when treatment is commenced has upon result. This is shown in table 9. In order to take into consideration the factor of time in studying this table it should be mentioned that the average time since discharge of the 1,747 is four years.

Among those admitted as incipient, the percentage who are now working is 81.81, while in the far-advanced stage of the disease it is 25.88. As regards failures to respond to treatment, of those admitted in the incipient stage 4.91 per cent are now dead, while of those admitted in the far-advanced stage 49.15 per cent are now dead.

TABLE 9

Stages and results on 1,747 patients after an average period of four years from discharge

CLASSIFICATION ON ADMISSION	TOTAL DISCHARGED ALIVE	PER CENT OF WHOLE	WELL AND WORKING		SYMPTOMS AND LIGHT WORK		UNABLE TO WORK		DIED		UNHEARD OF		DIED IN SANATORIUM	GRAND TOTAL OF DISCHARGES
			Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent		
Clinical														
Incipient.....	372	21.29	257	69.08	50	13.44	30	8.06	17	4.56	18	4.83		372
Moderately advanced....	472	27.01	283	59.96	54	11.44	78	16.52	29	6.14	28	5.93	9	481
Far advanced..	218	12.53	74	33.94	32	14.67	48	22.01	52	23.85	12	5.50	32	250
Bacillary														
Incipient.....	35	2.00	20	57.14	6	17.14	5	14.28	3	8.57	1	2.85		35
Moderately advanced....	115	6.57	35	30.43	11	9.56	31	26.95	36	31.30	2	1.73	3	118
Far advanced..	435	24.89	37	8.50	27	6.20	95	21.83	269	61.83	7	1.14	151	586
Nonpulmonary	100	5.72	56	56.00	10	10.00	26	26.00	5	5.00	3	3.00	11	111
	1,747		762	43.61	190	10.87	313	17.91	411	23.52	71	4.06	206	1,953

In separating the clinical cases from the bacillary it was found that among those admitted in the same stage of the disease there were three times as many clinical as bacillary cases that were well and working.

MORTALITY FROM DATE OF ADMISSION

Of the 1,953 tuberculosis patients admitted to the sanatorium and discharged prior to December 31, 1924, 617, or 31.59 per cent, are now dead. Of this number 26 died of a nontuberculous cause, making the

tuberculosis deaths 591, or 30.26 per cent. Of the 591, 205,[2] or 10.49 per cent, died in the sanatorium during their first period of treatment and an additional 19.75 per cent have died since their first discharge.

A study was also made of the relation of condition on admission to mortality.

Of those who died from tuberculosis, only 13.53 per cent were admitted to the sanatorium in the incipient and moderately advanced stages, while 83.73 per cent were admitted in the far-advanced stage. Furthermore, among those who are dead, 19.60 per cent were clinical cases, that is, they had no bacilli in their sputum, while under treatment, and 77.66 per cent were bacillary.

TABLE 10

Condition on admission of 591 who died from tuberculosis

CLASSIFICATION	NUMBER DIED	PER CENT
Clinical I	8	1.35
Clinical II	32	5.41
Clinical III	76	12.84
Bacillary I	3	0.50
Bacillary II	37	6.27
Bacillary III	419	70.89
Nonpulmonary	16	2.70

MORTALITY FROM DATE OF DISCHARGE

Table 7 shows the percentage who have died since returning home, according to year of discharge: 411, or 23.52 per cent, of the 1,747 are dead, and 386, or 22.09 per cent, have died of tuberculosis.

It is of importance for physicians and others, who are endeavoring to cope with the problem of tuberculosis, to know what the expectancy of life is in the case of patients who fail to recover after discharge.

From table 11 it will be seen that, of all the deaths occurring among the 1,747 patients from one to eight years after discharge, more than 50 per cent occurred within the first year, and almost 75 per cent of the deaths occurred within the first two years, while nearly 90 per cent occurred within three years.

[2] One of the deaths in the sanatorium was from a nontuberculous cause.

SEX IN RELATION TO PROGNOSIS

It was considered that the relation of sex to prognosis might be of importance, and a study was made on this basis. Without consideration of condition on admission, it was found that out of 1,018 males

TABLE 11

Time after discharge in relation to death

TIME	NUMBER DIED	PER CENT
years		
Less than 1	207	53.54
1 to 2	92	23.83
2 to 3	41	10.62
3 to 4	24	6.26
4 to 5	16	4.14
5 to 6	5	1.29
6 to 7	1	0.25
7 and over		

TABLE 12

Age, sex and marital state of those who died after discharge

AGE	TOTAL	DEATHS	PER CENT	MALE	FEMALE	FEMALE MARRIED	FEMALE SINGLE
years							
Under 5	19	1	5.26	1			
5 to 9	68	1	1.47		1		1
10 to 14	108	13	12.03	1	12		12
15 to 19	220	43	19.54	17	26	5	21
20 to 24	368	96	26.08	49	47	28	19
25 to 29	340	90	26.43	57	33	25	8
30 to 34	235	59	25.10	40	19	19	
35 to 39	194	45	23.19	24	21	21	
40 to 44	104	16	15.37	10	6	5	1
45 to 49	43	4	9.30	3	1	1	
50 to 59	38	13	34.21	8	5	5	
60 to 69	9	5	55.55	4	1	1	
	1,747	386	22.61	213	172	110	62

who returned home 213, or 20.85 per cent, died. Out of 729 females, 172, or 23.59 per cent, died. From this it would seem that there is a slight difference in favor of males in prognosis with regard to sex.

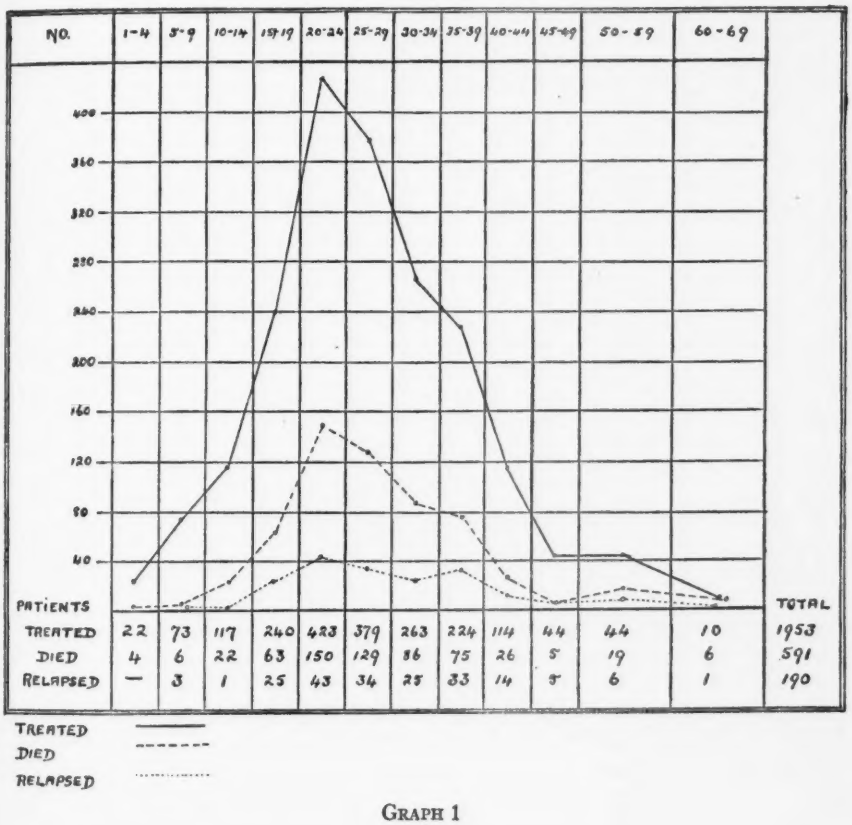
The marital state of females in relation to prognosis was also investigated, and it was found that, out of 358 women married prior to sana-

torium treatment, 110, or 30.72 per cent, had died, and, of 371 single women, 62, or 16.71 per cent, had died. Fifty of the 371 single women have married since discharge, and of this number only one has died.

OPERATIVE MORTALITY AMONG THE TUBERCULOUS

During treatment of 1,953 patients operations were performed on 23. There was no immediate mortality, although the postoperative mor-

AGE GROUPS OF PATIENTS TREATED IN RELATION TO RELAPSES AND DEATHS



PATIENTS	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-59	60-69	TOTAL
TREATED	22	73	117	240	423	379	263	224	114	44	44	10	1953
DIED	4	6	22	63	150	129	86	75	26	5	19	6	591
RELAPSED	—	3	1	25	43	34	23	33	14	5	6	1	190

TREATED ——————
DIED - - - - - - -
RELAPSED .....

GRAPH 1

tality was three. One of the deaths followed an operation for nasal obstruction, one resection of bowel, and one the removal of a ruptured appendix. The tuberculous condition was aggravated by operation, and the patients died from one to three months after operation.

Following discharge, 3 of the 1,747 who returned home had minor operations and 47 had major operations. There was no mortality following the minor operations. In case of the major operations the immediate mortality was 4 and the ultimate mortality one. It should be mentioned that one of the deaths was due to an emergency operation for ectopic gestation and another to a panhysterectomy.

Of the 68 major operations both before and after discharge the immediate mortality was 4, or 5.88 per cent, and the ultimate mortality was 8, or 11.76 per cent. Considering all things, it is really remarkable how well these tuberculosis patients have come through serious operations, at least half of which were emergency cases.

Graph 1 presents a clear picture of the relapses and deaths in relation to age.

COMPARISON WITH FOLLOW-UP RESULTS FOUND ELSEWHERE

It is difficult to compare any two groups on account of the number of factors that may modify results, important among which are age and time which has elapsed since discharge, in addition to such other factors as economic condition, occupation, sex, etc. Nevertheless, a group which has much in common with the present group studied is that of the 953 patients followed by the Metropolitan Life Insurance Company Sanatorium at Mt. McGregor, New York, inasmuch as the patients of both sanatoria have been discharged approximately the same length of time, that is, from one to seven years. It must also be borne in mind that the average period of treatment at Mt. McGregor was nine months, while the average period at Fort Qu'Appelle was six and a half months. Furthermore, the Mt. McGregor group was largely clerical, while the Fort Qu'Appelle group was largely agricultural. Table 13 compares the follow-up results secured by these two sanatoria.

Although in the Fort Qu'Appelle group a very large proportion were admitted in advanced stages, while in the Mt. McGregor group a very large percentage were admitted in the incipient stage, there was little difference in the follow-up results, when comparing them group by group. From this table it is evident that slightly better results were secured in the case of the Mt. McGregor patients in the incipient stage, 83.9 per cent of whom are shown as working, as compared with 81.8 per cent at Fort Qu'Appelle. Also, in the moderately advanced group 66.4 per cent of the Mt. McGregor patients are working, while 65.2 per cent of the Fort

Qu'Appelle group are working. Slightly better results were secured in the case of the advanced patients at Fort Qu'Appelle, where 26 per cent are working, compared with 20 per cent for Mt. McGregor.

The mortality is also very similar, for 3.1 per cent of the incipient cases of the Mt. McGregor group are dead, while the mortality at Fort Qu'Appelle is 4.9 per cent. In the moderately advanced group at Mt. McGregor 14.7 per cent are dead while at Fort Qu'Appelle 11.0 per cent are dead. In the far advanced group at Mt. McGregor 57.1 per cent are dead, while at Fort Qu'Appelle 49.1 per cent are dead; therefore, as regards mortality, better results were secured in the incipient group at Mt. McGregor, while in the moderately advanced and far-advanced groups better results were obtained at Fort Qu'Appelle.

TABLE 13

Comparison of follow-up results

CLASSIFICATION ON ADMISSION	FORT QU'APPELLE									MOUNT MCGREGOR								
	Total	Able to work		Unable to work		Died		Unheard of		Total	Able to work		Unable to work		Died		Unheard of	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
I	407	333	81.81	35	8.59	20	4.91	19	4.66	585	491	83.9	36	6.1	18	3.1	40	6.8
II	587	383	65.24	109	18.56	65	11.07	30	5.11	333	221	66.4	47	14.1	49	14.7	16	4.8
III	653	170	26.03	143	21.89	321	49.14	19	2.91	35	7	20.0	7	20.0	20	57.1	1	2.9

I = incipient; II = moderately advanced; III = far advanced.

In conclusion, it should be noted that in the application of any data derived from the study made of the Fort Qu'Appelle patients the reader must bear in mind that the total number (1,747) is small, as well as that the time since discharge is short, varying from one to seven years. Nevertheless, the time since discharge has been sufficiently long to cover the period during which the greater percentage of relapses and deaths occur; consequently, it is considered that the findings are of value in the guidance of antituberculosis activities.

SUMMARY

Of the Follow-up Information on 1,747 Tuberculosis Patients, One to Seven Years after Discharge from a Sanatorium

There were 1,953 patients, who were treated for active tuberculosis, discharged from the Fort Qu'Appelle Sanatorium between October 10,

1917, and December 31, 1924. Of these, 206, or 10 per cent, died in the sanatorium; the remaining 1,747 returned home and have since been "followed up." Of this number, 1,018 were males and 729 females, while 5 per cent of the 1,747 were nonpulmonary and 95 per cent were pulmonary cases. Of the pulmonary group, 97 per cent were of the chronic parenchymatous type.

Recoveries

Of the 1,747, 43 per cent are well and working.
10 per cent have symptoms and are doing light work.
17 per cent are unimproved and unable to work.
4 per cent are unheard of.
23 per cent have died of tuberculosis.
1 per cent have died of nontuberculous conditions.

Occupations

Of the 952 who are working, 57.25 per cent are males and 42.66 per cent females. All of the 407 women are engaged in indoor occupations. Of the 545 men, 61.28 per cent are engaged at outdoor and 37.61 per cent at indoor occupations.

Seventy-nine per cent returned to occupations which they followed prior to sanatorium treatment; 20 per cent changed their occupations; 8 per cent returned to similar occupations; 6 per cent changed from heavier to lighter occupations; and 6 per cent changed from outdoor to indoor occupations.

Living Conditions

Economic conditions subsequent to discharge were fair in the case of the 514, or 26 per cent, who were pensioners. In the case of the remainder, 80 per cent were unable to pay for their treatment in the sanatorium, and they must have been correspondingly embarrassed since returning home.

Relapses

Of the 1,747 followed, 190, or 10.87 per cent, have relapsed since discharge.[3]

[3] Relapse refers to those being "quiescent and able to work" or else "apparently arrested."

Of the relapses, 53 per cent occurred within one year, 76 per cent within two years, and 88 per cent within three years. The danger period is the first three years, and after-care should be concentrated on this period.

When insufficient treatment was given, the percentage of relapses showed an inverse relation to length of institutional treatment; the shorter the period of treatment the larger the percentage of relapses. Sufficient treatment is the best protection against recurrence.

When sufficient treatment was given the number of relapses was in proportion to the extent of the disease, and the percentage of relapses was greater, in proportion, among the bacillary cases.

A very small percentage of relapses occurred among patients in the age-groups under fifteen years, after that varying between 9 and 14 per cent, and showing no consistent relation to age-group.

Males, as a group, relapse more frequently than females, 14 per cent of the 1,018 males relapsing and only 4 per cent of the 729 females. Of the 545 males who worked, 24 per cent relapsed, and of the 407 females, 10 per cent relapsed.

More relapses occurred among the patients who returned to heavy occupations. The percentage of farmers who relapsed was over three times the average, and the percentage of laborers more than twice the average.

Among the 334 males engaged in outdoor occupations, 94, or 28 per cent, relapsed. Among the 205 males engaged in indoor occupations, 39, or 19 per cent, relapsed. From this study it would appear that indoor occupations are more suitable for tuberculous persons. This is probably because outdoor occupations in an agricultural community mean heavy labor.

Among 358 married women, 24, or 5 per cent, relapsed, just 1 per cent more than among single women. Child-bearing was unimportant in this group as regards cause of relapse.

Mortality

The mortality of males and females was found to favor males among the 1,747 cases. Of the males 20 per cent died since discharge, and 23 per cent of the females.

Mortality was below the average up to fifteen years, and just about the average, remaining very constant, from fifteen to forty. The mortality of those over fifty was nearly twice the average.

Without taking into consideration other factors, the prognosis for unmarried females was better than for the married ones. Thirty per cent of the married and 16 per cent of the unmarried died.

The home, family responsibilities and other factors affecting married women in this group appear to be of greater importance in prognosis than child-bearing. Only five deaths bore any relation to child-bearing following discharge.

As disease advances, the beneficial results of treatment diminish. Of those who died in the sanatorium, 88 per cent were in an advanced stage on admission, and of those who have died since discharge 77 per cent were advanced.

Of those admitted in the incipient stage, 81 per cent are working.

The time which has elapsed since discharge is a very important factor in the prognosis of tuberculous persons, since it was found that, of the dead, 53 per cent died within one year of discharge, 77 per cent within two years, and 87 per cent within three years.

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THE TREATMENT OF TUBERCULOUS LYMPHADENITIS AMONG AMERICAN INDIANS

A Preliminary Report

R. J. COLLINS AND G. L. LESLIE[1]

Scrofula, to use an old-fashioned term, has been more or less a characteristic manifestation of tuberculosis in the Indian race from the earliest period of which we have any statistics, however crude, of disease among the various tribes of the North American Continent. In fact, when one has occasion to think at all of tuberculosis among the Indians, one instinctively thinks of tuberculous adenitis, and of cervical involvement in particular.

The purpose of this short paper is to emphasize the value of certain conservative methods of treatment to which these cases of adenitis, however extensive, almost invariably respond in a satisfactory manner. Tuberculosis of all types is unduly prevalent among these people, the death-rate in 1920 in the United States being 6 per 1000, or 20 per cent of the total deaths from all causes. Nevertheless, although this prevalence is an indication of the Indians' low immunity, plenty of evidence has been adduced to show that the morbidity and mortality rates of the red race decrease rapidly with improved environment, and that at least the scrofulous types respond quickly to proper treatment.

It might be worth while to give a sketchy outline of the history of this condition, as found in the different tribes. In 1921 the National Tuberculosis Association, in conjunction with the Bureau of Indian Affairs of the United States, appointed a committee to ascertain the extent of tuberculosis among the Indian population. Incidentally, much literature was reviewed; and this revealed accounts of disease among the tribes dating as far back as 1633. Many of the accounts are conflicting, as there was no organized medical service prior to 1875. But the Jesuit Fathers among the various tribes speak of what they considered to be scrofula. LeJeunne in 1633 says that the Indians were nearly all at-

[1] Jordan Memorial Sanatorium, River Glade, New Brunswick, Canada.

tacked by this disease when young. Father LeMercier, in 1653, speaks of a child at Tadoussac "afflicted in a terrible manner with scrofula on his neck, his entire throat being eaten away by it." Thomas Williamson, about 1840, says of the Sioux of Minnesota that of those over 10 years of age who died of disease, one-half died of consumption, and scrofula was almost universal among women and children. Kober, in fourteen years' experience among a population of 5000 Indians in Modoc County, believed that they probably did not contract the disease from the whites, but that the introduction of cattle by the whites was an important factor, for previous to 1884 the children were all breast-fed, and only the adults were scrofulous. He states that the scarcity of food in 1874 compelled the Indians in Nevada to consume the flesh of domestic animals that had died. Nor was this an isolated instance. Everywhere the encroachment of the whites had meant scarcity of game and other food for the inland Indians, and the resulting semistarvation often forced them to this revolting practice (1).

Several interesting conclusions were reached in the committee's report. Not the least important was that the prevalence of tuberculosis among the Indians was not so much due to the fact that the disease attacked them with a racial preference, but that the advent and encroachment of the white man created difficult economic conditions, and the resulting struggle for existence favored the spread of the disease. This conclusion detracts somewhat from the popular belief that a marked racial predisposition is more to blame than anything else for the widespread tuberculosis among them, and relieves the emphasis laid on the fact that the Indian has undergone a comparatively short period of tuberculization. In a way it parallels the record of the American Negro, who, well-housed and well-fed under bondage, suffered from tuberculosis relatively little more than the whites, but whose mortality rates shot up with great rapidity following their liberation and the consequent unfavorable economic conditions.

It was also noticed that in many cases there was a wide difference in morbidity rates among different tribes of Indians. It was found that there was a direct ratio between the extent of the disease and the degree to which the living conditions of certain tribes approximated the more sanitary conditions of the whites.

As to the prevalence of adenitis among the Indians of Canada, a recent survey undertaken by the Province of Saskatchewan, in which 1,346 school children, white and Indians, were examined, best illustrates this.

Among the whites no lymph nodes were found large enough to require treatment or to justify the diagnosis of tuberculosis; but among the Indians enlarged and discharging lymph nodes were exceedingly common. The tuberculin test also showed that 92.5 per cent of the Indian children were infected, as compared with 54 per cent for children of all other racial groups (2).

In connection with this very high percentage of infection an interesting discovery was made. The herds providing the sole supply of milk to the children of the two Indian schools examined, when tested, were found to react in a high percentage, 50 per cent of one herd being positive. Of the children in the school supplied with milk by that herd, 91.8 per cent reacted to tuberculin. This would seem, then, to be additional evidence in favor of the contention that the bovine bacillus is responsible for a certain percentage of these infections. Park and Krumwiede (3) have estimated that at least 25 per cent of the tuberculosis of bones, lymph nodes and joints among children is due to the bovine bacillus.

In many cases tuberculosis supervenes in lymph nodes which are enlarged as a result of chronic septic irritation. Therefore such conditions as enlarged tonsils, adenoids, carious teeth, middle-ear disease and other unhealthy conditions about the head, which are commonly found in school-children surveys, undoubtedly predispose to tuberculous adenitis. In a recent survey of 600 school children in New Brunswick it was found that practically 40 per cent had cervical lymph-node enlargement, varying from the size of a small pea to that of a cherry, although in no case was the diagnosis of tuberculosis justified. No Indian children were examined, but oral conditions are just as rife, if not more so, than among the whites. This, in conjunction with their low resistance and none too sanitary living conditions, is doubtless as important a factor as any in the prevalence of tuberculous adenitis.

Another fact that provides material for reflection is brought out by the Indian census returns of the last twenty years. Contrary to the popular belief that the Indians are a decadent race, that disease is getting the better of them, and that extinction is only a matter of time, statistics prove their population to be on the increase. In 1900 the Indian population of the United States was approximately 270,000. In 1921 the figure stood at 341,000, and a still later estimate gives the population for 1925 as about 350,000. In Canada the Department of Indian Affairs placed the Indian population in 1924 at approximately 105,000, an increase over the figure for 1916. These figures clearly indicate that the

efforts of the two Governments, directed through their Departments of Indian Affairs, to provide adequate health inspection and to better living conditions on the Reserves, are succeeding. There were no reliable medical statistics for Indians in the United States until 1911. In 1912 the Indian tuberculosis death-rate was 10.4 per 1000, or 32 per cent of the total deaths, while in 1920 it was 6 per 1000, or 20 per cent of the total deaths.

There are about 1600 Indians on the various reservations in New Brunswick. These are chiefly of the Micmac race, with a few Malecites. Both are of Algonkin stock. Morbidity rates for these Indians are lacking, but periodical medical inspections on the reservations are responsible for the frequent admission to the sanatoria of children, and occasionally adults, suffering from tuberculous adenitis.

In many cases only one lymph node may be affected, usually below the angle of the mandible. This may reach the size of a hazel-nut. More often, several lymph nodes, on one or both sides of the neck, are affected. If the disease begins in the submaxillary nodes, it tends to spread to those along the carotid sheath. The usual sequel to involvement of the occipital and posterior auricular nodes is a spread to those along the posterior border of the sternomastoid, in many cases resulting in a mass of enlarged lymph nodes at the base of the posteror triangle.

As to the treatment of these conditions, there are those who, mindful of the danger of extension of the disease, rapid destruction of tissue and mixed infection, believe that best results are obtained by excision. But the uniformly good and permanent results that may be obtained in institutions, where the roentgen-ray and Alpine sun-lamp can be properly used in conjunction, rather discountenances the more radical treatment, apart from the fact that it is almost impossible to remove all the infected nodes surgically.

We have had very satisfactory results in the treatment of these cases by sun-lamp and X-ray therapy. Daily exposures to the Alpine lamp, supplemented in summer by sun-baths whenever possible, effect noticeable improvement in a very short time, and it is rare to see any progress of the condition after this treatment has been started. Exposures are graduated from 3 minutes the first day up to a maximum of 30 minutes, on both sides of the neck if necessary, the lamp being set at a distance of 30 inches. Of late we have been cutting down the time and the distance, at the same time increasing the concentration of the rays. The exposure is modified by individual peculiarities of reaction, such as burning, shock and fever.

This daily exposure to the ultraviolet rays is supplemented by roentgen-ray therapy,—one treatment a week, interrupted at certain intervals to lessen the danger of overexposure. The subject is covered with a heavy rubber apron, with a slit through which the X-ray tube may be focused on the lymph nodes at a 15-inch distance. An initial treatment of two minutes is given, with a kilovoltage of 175 and milliamperage of 5, filtered through 3 mm. of aluminium. The third treatment is for a 3-minute period, and later applications remain at that. We have found that weekly treatments for a shorter interval give better results than longer exposures every two or three weeks.

In the meantime, sloughing areas are kept clean with sterile dressings. The contents of lymph nodes that have proceeded to liquefaction are withdrawn through needles, when necessary, this procedure often forestalling further sinus-formation, as the suppurative process usually improves rapidly with the other therapeutic measures.

The following are several case reports which illustrate briefly the effect of the above-mentioned treatment on some of the more extensive types of adenitis met with:

Case 1: A Micmac, aged 5 years, male, admitted July, 1924, with the submaxillary lymph nodes on both sides involved, those below the angle of mandible on both sides discharging. Practically all the nodes along the carotid sheaths, as well as those in the posterior triangles, were also involved. The patient was put on Alpine sun-lamp exposures daily, asssociated with exposures to the direct sun. He improved steadily, and was about ready for discharge in February, 1925, when he contracted measles, and following this had a marked exacerbation of his disease for more than a month. It was found necessary to aspirate the contents of a submental abscess on several occasions. The patient was given a course of twelve X-ray treatments, along with sun-lamp exposures, and steady improvement was noted. He was discharged the latter part of 1925, apparently cured.

Case 2.. A Micmac, aged 8, female, admitted in September, 1924, with three large discharging ulcers on the right side of the neck, and a recently healed area on the left side. The submaxillary nodes on both sides, with those along the right carotid sheath, and a few in the posterior triangles, were also involved. Exposures to sun-lamp and direct sun were started, with a course of roentgen-ray treatment. Gradual improvement was noted from the first, the ulcers slowly healing over, and the nodes decreasing in size. The patient was discharged, July, 1925, apparently cured.

Case 3: A Malecite, aged 12, female, admitted in July, 1925, with a two months' history of enlarging lymph nodes. The anterior and posterior nodes

were involved, chiefly on the right side, and the submaxillary nodes on both sides, with several discharging sinuses and ulcers. There were also two nodes in the left axilla about the size of cherries. Under a course of X-ray treatment, and exposure to the sun, the ulcers have completely healed, and the lymph nodes, including those in the axilla, have almost entirely subsided. The patient is still in the institution undergoing treatment for moderately advanced pulmonary tuberculosis.

Case 4: A Malecite, aged 19, female, married, admitted in April, 1925, with a history of gradual enlargement of the lymph nodes for about three months. In the posterior triangle on the right side of the neck were three or four nodes about the size of a cherry, and several smaller ones. In the left axilla there was a node about the size of a walnut, with periadenitis and marked tenderness. There was no pulmonary disease. The patient was at once started on Alpine sun-lamp treatment, the whole body being exposed. She was also given weekly X-ray treatments, particular attention being paid to the axillary condition. Rapid improvement was noted from the outset, the periadenitis and tenderness disappearing in three weeks. By the latter part of June the lymph nodes had entirely subsided, that in the axilla being no more than palpable.

The usual history is one of quite rapid enlargement, proceeding in a few weeks to suppuration and discharge. In practically every case there is disease elsewhere in the family. A parent has pulmonary tuberculosis, or the children in the family have lymph-node disease. In a recent instance two sisters died of tuberculosis, and four others have tuberculous lymphadenitis.

Recurrences of the adenitis are by no means rare. This cannot be taken, however, as an indication that treatment was ineffective, for the child returns to unsanitary, reinfecting living conditions on the Reserve. We have also noted on several occasions how immediate and marked an exacerbation will follow any catarrhal infectious disease, especially measles. As a rule, however, it can be expected that a thorough course of such conservative treatment as that outlined above will effect in the great majority of cases a practical cure. It is now generally considered, at least in sanatoria, that the surgical removal of lymph nodes is uncalled for. In fact, in those cases which have been operated upon, an after-course of X-ray and sun-lamp therapy is very often found necessary.

At present we have eight Indians, mostly children, undergoing treatment for tuberculous adenitis of varying severity. Two are complicated by pulmonary disease. At a later date we wish to make a more detailed report of the end-results of treatment in these cases.

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DEDUCTIONS DRAWN FROM EIGHT YEARS OF TUBERCULOSIS WORK AMONG NEGROES

H. G. CARTER[1]

In Virginia ten years ago there was not a single bed for the treatment of tuberculosis among Negroes except those in the hospital for the insane and in the penitentiary, in both of which institutions adequate provision for the tuberculous had been made. The health authorities were not indifferent to this situation, but they knew it to be important, before establishing a sanatorium for Negroes, to be sure that the leaders of the colored people would be in full sympathy with the work and would urge their fellow-men to take advantage of the opportunity to be afforded by the State.

Numerous conferences were held with leading Negro organizations and associations of people interested in work among the Negroes. Before embarking upon the experiment of building and equipping a sanatorium there were two points to be decided, so far as decision in advance was possible: first, would the Negro leave his work and home while in the early stages of the disease and go to the distant hospital for treatment, that is, in sufficient numbers to make the investment worth while; and, second, would the Negro have enough resistance to justify building and conducting a sanatorium?

The outcome of these numerous discussions was a conclusion in the nature of a compromise. It was decided to make an appeal to the Legislature for a sanatorium on an experimental basis, building unit by unit, as the demand grew: and the first unit of 30 beds was opened April 22, 1918.

The formal opening was preceded by a great deal of publicity work on the part of the Virginia Tuberculosis Association, then being directed by Miss Agnes D. Randolph. Within three months the 30 beds were full and the second unit started. The demand for additional beds has continued, and we have to-day a 150-bed institution, well-built and well-equipped. We have always kept our beds filled, and are

[1] Deceased. Formerly Medical Superintendent of Piedmont Sanatorium, Burkeville, Virginia.

never without a waiting-list. Sometimes this list has been long enough to ensure a filled sanatorium for three months in advance.

From our waiting-list we select the most suitable cases; but whenever that list is low, and we are confronted with the dilemma of unfilled beds or unsuitable cases, we choose the latter and then we get "top heavy" with advanced cases.

Thus, experience easily proved that the Negro would go to a sanatorium; and fortunately we were soon able to demonstrate that tuberculosis in the Negro could be arrested. This demand was brought to the attention of all Negro leaders in the State,—ministers, doctors, and other prominent men, to whom the general mass of the race looks for guidance; but we impressed upon all these the importance of early treatment.

I believe that a factor which largely contributed to our success was the employment of arrested cases at the sanatorium whenever practicable. It means so much to the unfortunate, who has all his life heard that tuberculosis is incurable, to be thrown daily into intimate contact with those who have been cured; and I think we owe to those old patients, who have been employed as nurses, orderlies, waiters or in other posts, more credit for our success than to any other factor. Their loyalty to the institution, their zeal, their work, and above all the concrete object lesson which they furnish to the discouraged, are of incalculable value. They form a regular colony with their own organizations, amusements and entertainments. Through their efforts we have built and equipped a very creditable little church, where they hold religious services, Sunday-school, prayer meetings, and entertainments. They have an excellent glee-club and have twice broadcast their songs.

Contributing to our success have been the field clinics formerly conducted by the Virginia Tuberculosis Association and now conducted by the State Board of Health. These clinics give us a large percentage of our cases, and serve to educate the public and the medical profession in the early recognition of tuberculosis. The support given by the influential Negro organizations has also been a most important factor. The Negro ministers and leading Negro doctors have always supported our work most enthusiastically.

On the other hand, a serious handicap has been the inability of many who practise medicine among the Negroes to diagnose early tuberculosis. We receive applications marked "incipient," which later prove upon examination to be far advanced. In some cases this discrepancy may

be explained by rapid progression of the disease, but in others the history shows a tuberculous condition present for several years. The recognition of early tuberculosis on the part of the practising physician is, however, gradually improving; and I believe that the field clinics are largely responsible for this improvement. Another handicap is the normal financial condition of the Negro. Negroes are lavish spenders. Few make provision for sickness, except possibly through a short-time insurance policy. We have also the difficulties of domestic differences calling them back home, yet this is probably no worse with us than in the white institutions.

Conversely, the happy, ease-loving disposition of the Negro is an asset while he is travelling the long road to recovery; but when this ease-loving goes to the point of irresponsibility and inability to grasp a serious situation it becomes a decided handicap. This is especially true of discharged patients. Unless they understand the seriousness of their condition their improvement is of short duration. They are so prone to go back to old habits and to unsuitable occupations that their mortality rate after leaving the sanatorium is frightfully high. In our last report we show 85 per cent of our minimal cases and 71 per cent of our moderately advanced cases improved, and 29 per cent of our advanced cases improved.

The results for the first two classes compare very favorably with those at the two State sanatoria for white people, but the advanced class shows only 29 per cent improved, while at Blue Ridge the percentage was 55 and at Catawba 60. By our selective policy, followed as far as practicable, we have been able to avoid the "vicious circle" of too many sick cases, too many deaths, the more deaths the fewer early cases and the more advanced cases, the more advanced cases the more deaths.

We began our work believing that there must be something approximating the truth in the widespread belief throughout the South that the mulatto has no resistance against disease and especially against tuberculosis. To our surprise our first annual report showed better results with the mulatto. I thought that this might be due to the small number of cases, and awaited with interest our second annual tabulation. This showed the same result; and not only did it show better results for the mulatto than for the black, but we divided our cases into black mulatto, dark mulatto, and light mulatto, and found that the light mulatto shows best where the black shows worst, the dark mulatto occupying a middle group.

The same results have been shown now for eight consecutive years; and I think we have demonstrated beyond doubt that the mulatto has greater resistance. There is certainly no doubt that this is true for the patients at our institution.

To what should these results be attributed,—environment or heredity? I thought at first that environment might have something to do with it, and I wrote numerous personal letters to social workers throughout the State. Answers to these show the consensus of opinion to be that environment of the mulatto and the black are practically identical. Eliminating this factor, it would seem, therefore, most probable that the difference in resistance, in so far as the mulatto may be concerned, must be attributed to white ancestry. A comparison of results at our institution with the two institutions in our State for whites shows our results to be not so good as with the others; but when we compare our light mulatto with the whites we note a near approach to parity.

Age-records furnish another argument for this view. The average age of our patients is less than the average age in the white institutions; and the average age of our mulattoes is higher than the average age of our blacks. If we had not discredited environment as a factor we might say that the black, through unsatisfactory environment, had received a more massive infection than the white, who had been naturally immunized by small doses; but with similar environment the black Negro is at a disadvantage when compared with the mulatto; and the death-age for the black is lower than for the mulatto. I am satisfied that this is to be accounted for through inherited resistance acquired by contact with the disease.

The high percentage of syphilis in our institution has afforded an excellent opportunity for studying pulmonary syphilis. Some time ago I wondered greatly at the scepticism of some of the best writers on tuberculosis regarding the occurrence of pulmonary syphilis, but I have found that it is indeed a rather difficult task absolutely to tag a case "pulmonary syphilis."

In our 1,700 cases we have had 171 cases of syphilis; of these 171 we have diagnosed pulmonary syphilis in 7. Our requirements for making a diagnosis of pulmonary syphilis are:

First, they must show definite parenchymatous lung disease.

Second, the sputum must be persistently negative for tubercle bacilli.

Third, the blood must show a 4+ Wassermann with a history of syphilitic infection.

Fourth, before definite diagnosis is made the therapeutic test is applied and the case must improve under vigorous antisyphilitic treatment.

We have had 7 cases to meet these requirements. We have had a number of patients with suspicious lung lesion and positive Wassermann, cough and elevation of temperature, who would clear up almost immediately under syphilitic treatment. We did not call them pulmonary syphilis because the lung lesion was not definite enough. We assumed that we were dealing with uncomplicated syphilis. We have had other cases that have had all the above requirements except that they did not improve under antisyphilitic treatment. We did not class them as pulmonary syphilis.

Several of these 7 cases have been checked by X-ray plates taken in series, and they showed a clearing under antisyphilitic treatment. These X-ray plates show nothing pathognomonic; for the most part they showed basic lesion not typical of tuberculosis. After finding a case that meets all requirements and clears rapidly under antisyphilitic treatment, one feels that the case is still an unimproved one; and I can readily understand why a noted roentgenologist wrote me some time ago, after having examined a series of plates of one of our cases of pulmonary syphilis, that while the plates were auto-typical of tuberculosis, he could not say definitely that it was syphilis because he had never seen a case of pulmonary syphilis. Our experience with tuberculosis complicated by general syphilis is that prognosis is thereby rendered more grave, regardless of which infection has antedated the other.

Our institution is situated just within the region infected by hookworm, and we draw heavily from some of the counties in the southern part of the State where the incidence of tuberculosis is very high. Prior to engaging in this work I had always thought that hookworm played a very important part in tuberculosis among the Negroes. Practically all of them go barefooted; and in the rural districts they have unsanitary privies. Seeped vitality in addition to the prolonged duration of hookworm would form an ideal complication for the development of tuberculosis. Again my theories were disproved so far as the Negro is concerned.

We find the ratio of hookworm infection among the Negroes who have broken down with tuberculosis to be less than 1 per cent, although, as stated above, we draw heavily from some districts where hookworm infection ranges as high as 35 per cent. I expressed my surprise at

these findings in a paper recently read before the Virginia Medical Association, and among those discussing the paper was Dr. W. A. Brumfield. Dr. Brumfield was for some years engaged in hookworm work in the South, and in his discussion he said that had I been a field-worker in hookworm work I would not have been so surprised at my findings; that it was a well-known fact among those workers that hookworm in the Negro was more or less a negligible factor among the black Negroes, and that the mulatto showed some infection, but a very small percentage when compared to the whites of the same locality. We have found only 7 cases of hookworm among 1,700 patients.

Diabetes is rarely found by us as a complication,—only five cases in 1,700 patients.

Laryngitis, enteritis and adenitis are all rather common tuberculous complications, especially in the advanced cases, but I have no statistics to show that these complications are any more or less common than they would be in an institution for the whites admitting the same type of cases.

We have noted that fistula-in-ano is a less frequent complication with us than in institutions for the white race. We have recorded only 11 cases in our 1,700 patients.

Spontaneous pneumothorax has been diagnosed by us in 17 cases, and 8 of these cases proved fatal, while 8 made a partial or complete recovery. All occurred in far-advanced cases.

One rather interesting fact, which I have noted, is the immediate fatality from hemorrhage. I never saw a patient, who was up and about, die in a hemorrhage until I took up this work among the Negroes. We have had 14 such deaths in a total of 211 patients in the last eight years. We do not include in this number those cases that are slowly dying, and whose life is snuffed out by a small hemorrhage, when we say we have had 14 deaths from hemorrhage. We mean that the cases were up and on exercise, and died during the hemorrhage and not of any complication following it. I have talked with a number of superintendents of institutions for whites, and many of them say that they never have seen such a case in a white man.

We have the usual nontuberculous complications that are found in institutions for whites. There have been 10 cases of lung abscess, 5 of malignant tumor, 2 of bronchiectasis, and 7 of pulmonary syphilis, as noted above.

We have discharged as improved approximately 50 per cent of the

cases that have entered the institution. A great many of these went home to their old environment, old work and old amusement, and, although it had been demonstrated to them conclusively that satisfactory environment, food and rest will cure their disease, they just seem to forget the past, disregard the future, and live for the present. These cases are short-lived, and the termination is due not to their lowered resistance but to their disposition. The old saying that "one gets well or dies of tuberculosis more as a result of what he has above his collar than what he has below" is certainly true of a great many Negroes. A creditable percentage of them, however, and in this percentage we find the really worth-while Negroes, realize the seriousness of the situation and try to follow instructions carefully.

These continue to live and improve; and we have such cases scattered all over the State of Virginia, men who are alive and working. They are always quite willing to drive many miles to be examined at the free clinics that are held throughout the State by the Bureau of Tuberculosis Education, under the State Board of Health. They are also quite willing at all times to get up at any meeting, although apparently perfectly well, and tell an audience that they had tuberculosis, have been treated, and are now cured. In this trait of character they would put to shame so many of our white patients who, after having been cured of tuberculosis, hold in perpetual disfavor the doctor who made the diagnosis, claiming that a serious mistake was made. I have never seen an instance of this kind in our colored patients.

Clinically, I find that the percentage of miliary tuberculosis is high among the Negroes, and it is quite common to have a case that has been doing fairly well suddenly become miliary in type. We have a good deal of so called tuberculous pneumonia in which the X-ray shows large caseous spots. We note on our X-ray plates that, even in those cases that are improving under treatment, there is less fibrosis than may be found in the whites. We do, however, find well walled-off cavities and they have considerable fibrosis. We have some cases of this kind engaged at the sanatorium as employees.

When I hear anyone make the statement that tuberculosis in the Negro is not curable I know that his experience with tuberculosis in the Negro is limited. I have heard such statements made on such insufficient evidence as that the X-ray plate does not show fibrosis. It is entirely true that the mortality rate of the sanatorium ex-patient is high, but this is not due as much to resistance as to the disposition of

the Negro. If I were to undertake a program of tuberculosis work among the Negroes of any city I would first see that a good clinic was established for the diagnosis of early tuberculosis. I would then get in touch with the Negro leaders of that city, especially the ministers, and impress upon them the importance of the early treatment of tuberculosis. This would create a demand for beds for the treatment of the diseased.

Most cities have well-established places for the segregation of hopeless advanced cases. I do not think that those cases intended for treatment should be connected in any way with an institution for segregation. Furthermore, I am of the very decided opinion that the Negro had rather have an institution of his own and not be treated with the white man. When these tuberculous patients get on exercise and begin to take an active interest in life they want to form their own organizations, arrange their own programs for amusement, and, in general, conduct themselves in their customary way.

Another very important fact to consider, in building a sanatorium for the treatment of tuberculosis in the Negro, is not to get beyond the educational work. I mean by that, never to build beds faster than there is demand for them. A waiting-list should always be kept, in order that the superintendent of the institution may be able to pick the type of case that is suitable. I do not consider that any sanatorium is worth while unless the patients of that institution are drilled in tuberculosis from every standpoint. We have weekly lectures given by our resident physician or medical director. It is compulsory for the patient to attend these lectures, and in our rule-book we have fifty questions at the end of the book that all patients are supposed to be able to answer before leaving the institution. In these lectures we try to drill into the patient all about how he received his infection, how and why it spreads; all about relapses and how to avoid them, and the danger-signals preceding a relapse; and we feel, when the patients leave us, that, even if they disregard what they know, we have done our duty by them.

As I stated at the beginning of this paper, I prefer to employ arrested cases to care for the sick patients. Under these conditions the Negroes will go to a sanatorium for the treatment of tuberculosis, and they will go in the early stages. However, they are very quick to leave when conditions do not suit them.

I know of one institution, well-built, well-equipped and well-staffed,

built for the treatment of tuberculosis in the Negro, in which the whole unit of 150 beds was built at one time and all cases applying for treatment were admitted. The result was a very high mortality rate; and to-day not more than one-third of the beds in that institution are filled, although it draws from a Negro population quite as large as the one we draw from, and it is possibly better built and better equipped than is ours. Its mistake was in admitting so many cases, especially in the early life of the institution.

CONCLUSIONS

1. Tuberculosis in the Negro is curable.
2. He will accept sanatorium treatment readily and gratefully if it is given under the proper conditions.
3. His resistance is not up to the standard of the white man's, and possibly will not be for many years.
4. The light mulatto shows a much better resistance to the disease than the black Negro, but even his resistance is not as high as that of the white man.

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THE VARIABILITY OF LOCALIZATION OF TUBERCULOSIS IN THE ORGANS OF DIFFERENT ANIMALS[1]

I. QUANTITATIVE RELATIONS IN THE RABBIT, GUINEA PIG, DOG AND MONKEY

H. J. CORPER AND MAX B. LURIE

Tuberculosis, while affecting under certain circumstances almost every organ of the human or animal economy, seems, however, to select certain preferred sites of localization in the different animal species, regardless of the mode of infection. This circumstance has taxed the ingenuity of investigators in their seeking a possible explanation for these apparent incongruities of organic involvement. The text-books and literature are wont to dispense with the findings merely as facts, and thus record innumerable individual observations without any apparent correlation.

In the rabbit the lung is the organ most commonly involved after infection with either human or bovine tubercle bacilli, while the liver usually escapes (1). Spontaneous disease is rare in this animal, but the rabbit succumbs quickly to inoculation with bovine bacilli with generalized disease, while, especially after intravenous inoculation, human bacilli produce an involvement limited almost entirely to the lungs.

Of all the ordinary laboratory animals the guinea pig is highly susceptible to both human and bovine bacilli; and, regardless of the mode of infection, the spleen suffers the most striking tuberculous involvement, becoming tremendously enlarged and necrotic. The dog is infected only with difficulty (2). In tuberculous dogs the lesions are for the most part found confined to the lungs, pleura, liver and kidneys, and in the abdominal lymph nodes. The spleen is almost always exempt.

The monkey, like the guinea pig, is very susceptible to tuberculous infection spontaneously and by inoculation. A generalized disease, involving many of the organs including the lungs, follows both human and bovine infection. de Haan (3) believes the lungs to be a site of predilection of the disease after feeding tubercle bacilli to monkeys. Cobbett (4), in tabulating the comparative susceptibility of various animals to the two types of mammalian tuberculosis, considers the guinea pig and

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

monkey about equally susceptible to human and bovine bacilli (rather more to the latter), the dog equally susceptible to both, and the rabbit more susceptible to the bovine bacillus. This, in general, summarizes the findings recorded in a voluminous literature; and, while there are a few divergences of opinion, little concerted effort has been directed toward correlating the findings as to tuberculous involvement of the various organs, or to explain the differences or similarities of the involvement in the several animal species. In highly susceptible species, or with large enough infecting "doses" of virulent tubercle bacilli in comparatively insusceptible animals, there usually results a metastatic disease of general nature in the majority of cases, regardless of the method of infection. In these cases, however, the quantitative relations of the seeding of the individual organs are entirely unknown, because of an intermittent or continuous small deposition of bacilli from some rapidly progressing or disintegrating lesion elsewhere in the body, in most cases the primary site of infection.

The method best suited to obviate, as far as possible, the unknown factor in organic infection is obviously that of intravenous injection; and this was therefore chosen for the purpose of comparing the susceptibility of the different organs of various animal species to tuberculosis. In order to compare the tuberculous involvement of the organs, rabbits, guinea pigs, dogs and monkeys were given intravenous injections of different doses of virulent human and bovine tubercle bacilli. The rabbits and dogs were injected into the marginal ear vein, while the guinea pigs received the bacilli into the jugular vein, and the monkeys into the femoral vein. The animals were killed for examination after different definite intervals of time, or in some cases they were examined after dying from natural causes. Careful, complete autopsies were performed in each case, in order to note the quantity of tuberculosis in each organ by estimating the number and size of the tubercles macroscopically present. In recording the results the number of tubercles were noted by an integer and their size in millimetres by a second integer at the right of the first.

TUBERCULOSIS OF THE VARIOUS ORGANS IN THE RABBIT

In the rabbit the lung is the seat of the greatest amount of tuberculous involvement. This holds true whether the dose is enormous, as 1.0

mgm. of virulent bovine bacilli, or as small as 0.000,000,1 mgm. of the same virulent strain. After large doses, the animal dies in 2 to 4 weeks, and the lung is full of innumerable small tubercles about 1 mm. in diame-

TABLE 1

*The quantitative tuberculous involvement of the organs of rabbits at different intervals after the intravenous inoculation of tubercle bacilli**

INFECTING DOSE IN MGM. OF VIRULENT BOVINE BACILLI	RABBIT	SURVIVAL AFTER INOCULATION	LUNG	LIVER	SPLEEN	KIDNEY†
1.0	1 and 2	2 weeks	41§	0	0	0
	3 and 4	3 weeks	51	0	0	0
	5	25 days	51	0	0	0
	6	4 weeks	53	0	21	12
0.01	1 to 4	4 weeks	52	0	21	11
	5	5 weeks	53	0	0	0
	6 to 8	6 weeks	54	0	21	11
0.000,1	1 to 3	4 weeks	22	0	11	0
	4 and 5	6 and 7 weeks	34	0	11	0
	6	2 months	37	21	22	13
	7 and 8	10 and 12 weeks	56	0	22	21
0.000,000,1	1 and 2	3 weeks	12	0	0	0
	3 to 6	4 weeks	12	0	0	0
	7	5 weeks	12	0	0	0
	8	2 months	54	0	12	13

* No table with human tubercle bacilli is included, since the rabbit is highly resistant to this strain of tubercle bacilli, and with large doses given intravenously a predominantly pulmonary disease develops after long intervals of time. If other organs are involved the picture resembles that seen with small infecting doses of bovine bacilli.

† All the other organs except the bone-marrow are as a rule not involved macroscopically.

§ The number of tubercles is indicated by the left integer recorded as follows:

1 = a few, rare tubercles;

2 = moderate number of tubercles;

3 = numerous tubercles;

4 = a miliary tuberculosis distributed all over the organ;

5 = a massive disease with most of the parenchyma involved by the disease; and the size of the tubercle in millimetres by the right integer. Where the readings for several animals are included under one figure they are the average of all the animals included, and in the majority of cases the range of variations was within 1 point.

ter; in spite of this the remaining organs show no macroscopic evidence of tuberculosis at this time. From the fourth week and later after infection with moderate doses of tubercle bacilli, other organs, especially the spleen and kidney, show macroscopic tuberculous involvement; but

even after so long a time as three months the amount of tuberculosis developed in the lungs is far greater than that developed in any other organs. This points to the remarkable susceptibility of the lung of the rabbit to tubercle bacilli, and to a possible comparatively greater resistance of the other organs, provided the seeding in the lung is not greater (evidence for which will be presented in a later paper) than in any other organ.

In striking contrast to the marked tuberculous involvement of the lung is the slight hepatic tuberculosis that develops in this animal. Only after a long period of time does macroscopic tubercle-formation become apparent, and then only to a slight extent. In the majority of cases no visible tubercle-formation was noted.

Of the remaining organs studied, the spleen and kidney show more tuberculosis than the liver, and their size lies intermediate between the lung and liver if the latter develops tubercles. The tubercles in the spleen tend to be more numerous than they are in the kidney. No difference in the size of the tubercles in these two organs was noted. The spleen does not become appreciably enlarged as a result of the tuberculous involvement.

Some tubercle-formation is seen in the bone-marrow. None of the other organs develop macroscopic tuberculosis.

The microscopic study of the organs of rabbits corroborated the macroscopic findings; namely, the tubercles in the lung are by far the largest, and show the largest necrotic centres without tendency to fibrosis. The liver, on the other hand, shows the least tuberculosis, with a marked tendency to fibrosis and healing of the tubercles. The spleen, kidneys and bone-marrow show an amount of tuberculosis intermediate between that of the lung on the one hand and the liver on the other, which follows more or less the distribution of the bacilli to these organs.

TUBERCULOSIS OF THE ORGANS IN THE GUINEA PIG

Two weeks after the intravenous injection of virulent human and bovine tubercle bacilli, tuberculosis is apparent macroscopically only in the spleen and lung. With very small doses, such as, 0.000,000,01 mgm., the spleen alone shows macroscopic evidence of tuberculosis while the lung is spared. Irrespective of the dose up to 0.1 mgm., during a two-week interval the liver is free from tuberculosis.

Four weeks after infection, tuberculosis of the several organs is modified

by the size of the infecting dose. After large doses (0.1 mgm.) the lung is full of tubercles and the spleen is less involved than the lung, while the liver shows by far less involvement than either the lung or the spleen. After a smaller dose (0.001 mgm.) the lung develops distinctly more tuberculosis than the liver, but the spleen reveals the most involvement

TABLE 2

Amount of tuberculosis in the organs of the guinea pig at intervals following the intravenous inoculation of virulent bovine tubercle bacilli

PERIOD AFTER INFECTION	INFECTING DOSE IN MGM.	GUINEA PIG NUMBER	LUNG	TRACHEO-BRONCHIAL NODES	LIVER	SPLEEN§
Two weeks	0.1	1 to 4	42*	(3)†	0	4 (2)
	0.001	5 to 7	22	(3)	0	4 (3)
	0.000,01	9 and 10	11	(3)	0	2 (2)
	0.000,000,01	13 to 16	0	(1)	0	1 (1)
Four weeks	0.1	17 to 20	5	(4)	33	4 (6)
	0.001	21 to 24	33	(5)	22	4 (4)
	0.000,01	25 to 28	24	(6)	23	4 (3)
	0.000,000,01	29 to 32	13	(8)	12	4 (4)
Six weeks	0.001	37 to 40	33	(7)	41	5 (6)
	0.000,01	41 to 44	33	(9)	5	5 (7)
	0.000,000,01	45 to 47	22	(9)	21	5 (5)

* The left integer under lung, liver and spleen indicates:

1 = rare tubercle;
2 = moderate number of tubercles;
3 = numerous tubercles;
4 = miliary involvement;
5 = massive involvement.

The right integer indicates the size in millimetres of the individual tubercles; thus, 42 equals a miliary tuberculosis, the size of the individual tubercles being 2 mm.

The readings are the average for the several animals, as indicated under the same dose, the majority varying only within one point.

† The figures in brackets opposite the tracheobronchial nodes and the spleen indicate the increase in size of the organ above normal; thus, for the 4-week interval and 0.1 mgm. dose, the tracheobronchial nodes were increased to (4), four times their normal size, and the spleen 4 (6) showed a 4-miliary tuberculosis, with its size (6) six times normal.

§ In all these guinea pigs the kidney was practically negative.

comparatively. With decreasing infecting doses the spleen becomes increasingly more involved, comparatively, and the lung and liver tend to occupy opposite relations in tuberculous involvement. For example, after 0.000,000,01 mgm. the liver is equally or more involved than the lung. As a general rule, it may be stated that the more pronounced the

pulmonary involvement, the less is the tuberculosis developed in the liver and *vice versa*. There is no parallelism therefore between the pulmonary and hepatic tuberculosis in the guinea pig at this time. The significance of this discrepancy will be discussed in a later paper. In general, the amount of tuberculosis developed in the various organs of the guinea pig indicates that the lung is a much more favorable site for the development of tuberculosis than the liver, especially as is evident from the data of the first two weeks, after which the spleen of the guinea pig becomes the organ of greater tuberculous involvement.

TABLE 3

Tuberculosis in the organs of guinea pigs at intervals after the intravenous inoculation of virulent human tubercle bacilli

ORGAN	TIME INTERVAL BETWEEN INOCULATION AND EXAMINATION											
	2 weeks				4 weeks				6 weeks			
	Infecting dosage in milligrams											
	0.1	0.001	0.000,01	0.000,000,01	0.1	0.001	0.000,01	0.000,000,01	0.1	0.001	0.000,01	0.000,000,01
Lung	41	31	21	11	42	33	23	12	5	33	33	23
Tracheobronchial nodes	(2)	(3)	(2)	(2)	(3)	(5)	(5)	(6)	(3)	(4)	(6)	(4)
Liver	0	0	11	11	0	12	11	21	0	0	0	22
Spleen	4(3	4(3)	4(3)	4(3)	4(5)	4(6)	4(5)	4(4)	4(7)	4(5)	4(4)	4(4)
Kidney	0	0	0	0	0	0	0	0	0	0	0	0

Notes of table 2 apply to table 3 also.

Six Weeks after Intravenous Infection: None of the guinea pigs which received 0.1 mgm. of virulent bovine tubercle bacilli survived six weeks, while those receiving 0.1 mgm. of a virulent human strain survived beyond this period. This is in accord with the observations of Theobald Smith (5) that the guinea pig is more susceptible to the bovine than to the human strain of bacilli.

At the six-week interval, in general, with all infecting doses the relationship between the amount of tuberculosis found in the lung and liver is reversed. The liver tends to become massively involved through the coalescence of numerous small foci, while pulmonary disease is moderate. At this time the spleen presents the greatest tuberculous involvement.

The liver is the seat of the greatest fibroblastic changes. The entire surface often becomes corrugated, as a result of the replacement of

tuberculous tissue by connective tissue. No such marked fibrotic changes are noted in any other organ.

THE RELATION BETWEEN TUBERCULOSIS OF THE ORGANS RESULTING FROM INTRAVENOUS AND SUBCUTANEOUS INFECTION

In guinea pigs the spleen develops more tuberculosis following subcutaneous infection with tubercle bacilli than any other organ, while the liver exceeds in involvement that of the lung, which is the last of these organs to develop the disease. This discrepancy between the involvement following intravenous and subcutaneous infection in the guinea pig deserves consideration.

It is evident that if the seeding is identical to all the organs in question, following intravenous infection, there occurs an active inhibition of the tuberculosis in the liver as compared to that in the spleen and lung. It is evident that with a single intravascular introduction of tubercle bacilli the seeding of the various organs is, for the greater part, completed at once. Now, since the liver inhibits the tuberculosis more than the lung it follows that there will be a time when the pulmonary exceeds the hepatic disease. On the other hand, after subcutaneous infection there comes a time when there occur repeated small infections into the general circulation from the original or adjacent foci (6).

This, it seems is of some significance in causing the differences of involvement of the various organs, following the intravenous or subcutaneous inoculations of tubercle bacilli in the guinea pig.

Another striking finding is discerned when studying the tracheobronchial-node involvement in the guinea pig, following intravenous injection. A comparison of the amount of pulmonary disease and the enlargement of the tracheobronchial nodes brings out the fact that the greatest enlargement of these lymph nodes occurs with the smaller pulmonary involvement, and this is especially so with the smaller infecting doses. Thus, guinea pig 28, four weeks after the intravenous injection of 0.000,01 mgm. of virulent bovine tubercle bacilli, shows a few pulmonary tubercles of about 4 mm. size, while the tracheobronchial nodes are enlarged six times. On the other hand, guinea pig 20 which received 0.1 mgm. of virulent bovine tubercle bacilli, reveals a massive pulmonary disease with the lymph nodes only three times normal size. In explanation of this, it seems that when the infecting dose is large the tubercle

bacilli lodged in the lung form tubercles and obstruct the lymph channels draining to the tracheobronchial nodes. Tubercle bacilli circulating in the blood from whatever source and coming to the lung are arrested, and prevented from reaching the nodes when the original foci in the lungs are numerous. On the other hand, when the original infecting dose is small and the number of pulmonary foci few the "open lung" factor of Krause (7) and Miller (8) comes into play, and the circulating bacilli gain ready access to the pulmonary lymphatic channels and are carried without interruption to the tracheobronchial nodes, which become massively involved. Krause has shown that the tracheobronchial nodes do not drain bacilli from the lung alone but may remove them from the general circulation. This is borne out by the fact that the tracheobronchial nodes show evidence of tuberculosis a short time after infection by intravenous injection and when no pulmonary involvement is discerned.

As a general summary of the characteristic organic tuberculosis in the guinea pig following intravenous infection, there is noted a marked enlargement and tuberculous involvement of the spleen. The lung in the earlier stages of infection, up to the four-week interval, is the seat of more tuberculosis than the liver, but in the later stages of infection the hepatic involvement gains on the temporary lead of the lung, so that six weeks after infection the relation between the two sites of tuberculosis is reversed, and that present in the liver exceeds that in the lung. The kidney in the guinea pig rarely develops tuberculosis in contradistinction to the kidney in the rabbit.

TUBERCULOSIS OF THE ORGANS IN THE DOG

The dog is less susceptible to tuberculosis than is the guinea pig, monkey or rabbit. An amount of virulent tubercle bacilli which will cause a progressive and fatal disease in the guinea pig or a marked pulmonary involvement in the rabbit will, if given to the dog in amounts proportionate to body-weight, produce a slight pulmonary involvement, all the other organs remaining free from the disease even after 124 days. For example, it is noted that 0.000,01 mgm. of virulent bovine tubercle bacilli given to guinea pigs 41 to 44 inclusive, each animal weighing about a pound, results in the development, at the end of six weeks, of massive tuberculosis of the spleen and liver and extensive disease of the lungs;

TABLE 4

*Tuberculosis in the organs of dogs, at different intervals after the intravenous inoculation of virulent human and bovine bacilli**

DOSES IN MGM. PER POUND BODY-WEIGHT	BACILLI USED FOR INFECTING	DOG NUMBER	SURVIVAL AFTER INOCULATION IN DAYS	ORGANS				
				Lungs	Liver	Spleen	Kidney	Bone-marrow
0.5	Bovine virulent	26	22	21†	5p§	21	11	1p
		25	24	?	5p	?	0	—
		1	29	41	5p	5p	0	1p
		58	29	41	5p	0	11	—
		59	36	51	5p	11	11	3p
	Gluckson	9	28	41	5p	0	0	0
		10	30	41	5p	21	0	3p
0.1	Bovine virulent	53	31	41	51	0	0	—
		51	33	3p	4p	5p	0	2p
		3	34	42	5p	0	0	—
		22	36	42	5p	51	22	—
		24	40	41	5p	0	0	—
		4	42	41	5p	41	11	31
		49	47	42	5p	0	0	1p
		50	68	52	0	0	0	—
		52	68	41	0	0	0	1
	Gluckson	12	41	42	5p	0	0	0
		11	49	52	5p	0	0	1
0.001	Bovine virulent	6	30	12	0	0	0	—
		20	38	21	5p	0	0	—
		5	47	22	3p	0	0	0
		21	65	22	41	0	0	0
		48	93	32	0	0	0	0
		55	107	53	2p	0	0	0
		56	107	44	51	0	0	0
		57	114	25	4p	0	0	—
		47	107	11	0	0	0	—
	Gluckson	13	42	32	51	31	0	0
		14	110	21	0	0	0	—
0.000,01	Bovine virulent	18	38	11	0	0	0	—
		8	146	22	0	0	0	0
	Gluckson	15	42	11	0	0	0	
		16	124	11	0	0	0	

* This table is constructed on the basis of both the macroscopic and microscopic studies of the organs, since macroscopic examinations alone proved unsatisfactory, especially in studying the spleen.

† The markings (left and right integers) used in this table are similar to those in table 2.

§ The additional sign in this table "p" indicates that the size of the tubercle was only a fraction of a millimetre.

on the other hand, dogs 18 and 8, receiving the same dose of virulent bovine bacilli, and dogs 15 and 16, receiving the same amount of virulent human bacilli per pound of body-weight, developed only an occasional tubercle in the lung, the other organs remaining, as a rule, free from tuberculous involvement.

Unlike the rabbit and guinea pig, no difference was noted in the susceptibility of the dog to bovine and human strains of bacilli.

The development of tuberculosis of the various organs in the dog after the intravenous inoculation of tubercle bacilli is dependent upon the size of the dose. With large doses, 0.5 to 0.1 mgm. per pound of body-weight, the lung develops miliary tuberculosis, with the tubercles ranging in size from 1 to 2 mm. The liver, on the other hand, contains minute individual tubercles, scarcely visible, but so numerous and close together that there results a massive tuberculosis with little normal liver parenchyma remaining. The spleen with these large doses presents an inconstant involvement. The kidney shows a slight tuberculosis, while the bone-marrow develops a moderate amount. While the dog develops less renal tuberculosis than the rabbit, there is more involvement in the kidney of this animal than in the guinea pig.

With moderate doses of bacilli (0.001 mgm. per pound body-weight) the tendency is for the lung to develop quite an extensive tuberculosis, while the liver manifests either a complete absence of the disease or a massive involvement. Irrespective of the dose or the amount of tuberculosis, the individual tubercles in the lung are always larger than in the other organs. These observations make it evident that the factors accounting for tuberculosis in the liver of the dog are intricate. With moderate doses of tubercle bacilli, the spleen, kidney and bone-marrow usually fail to develop tuberculosis. This absence of splenic tuberculosis in the dog stands in contrast to the massive tuberculous involvement of this organ in the guinea pig and to the moderate tuberculosis developing in the rabbit's spleen.

With small doses of tubercle bacilli the lung alone develops a few tubercles, while all the other organs remain uninvolved.

In summarizing the tuberculosis occurring in the organs of the dog following the intravenous inoculation of tubercle bacilli, the liver stands out as the conspicuous organ in tuberculous involvement. The lung also develops a considerable amount of tuberculosis, while the spleen remains negative except after the intravenous inoculation of large doses

of bacilli, when the disease in this organ is only slight. It is evident that the lung in the dog offers a good soil for the development of tuberculosis from the fact that with small doses the lung alone develops the disease, while all the other organs escape it.

TUBERCULOSIS OF THE ORGANS IN THE MONKEY

The *Macacus rhesus* monkey is the most susceptible to tuberculosis of the four species of animals studied in this series of experiments. In

TABLE 5

Tuberculosis of organs in the Macacus rhesus monkey resulting from the intravenous inoculation of virulent bovine tubercle bacilli

INTRAVENOUS INFECTING DOSE IN MGM. OF VIRULENT BOVINE TUBERCLE BACILLI PER POUND BODY-WEIGHT	MONKEY NUMBER	DURATION OF LIFE IN DAYS AFTER INFECTION	ORGANS				
			Lung	Liver	Spleen	Bone-marrow	Kidney
0.1	V2	12	41*	4p	4p	41	0
	V3	14	31	4p	(?)	4p	0
	V4	16	22	0	0		0
	B8	23	32	4p	51	41	1p
	B9	25	33	5p	41 (3)	41	11
0.001	V1	26	33	51	41	31	11
	V5	34	54	1p	41	41	21
0.000,01	V6	32	23	51	52	32	12
	V7	24	42	51	51	51	11
	B10	51	5p	31	35	31	11
	B11	67	39	22	34 (5)	+?	11
0.000,000,001	B12	111	22	11	54	0	1
	B13	48	29	23	35	51	1

* The same markings are used in this table as in tables 2 and 3, and the additional "p" sign of table 4.

no other animal did there occur such widespread disease following the intravenous inoculation of tubercle bacilli; even the proverbial resistance of muscle was lacking in this animal. After large doses of human tubercle bacilli, involvement of muscle was noted in only three of the 26 monkeys infected intravenously. None of the animals infected with a bovine strain showed involvement of muscle. The pleural and peritoneal membranes are more frequently affected than the muscles, and the omentum becomes studded along the path of the vessels with many

small tubercles. Pleural and peritoneal effusions are common, even in the absence of visible tubercles. The pericardium and the arachnoid are rarely involved. Occasionally, the serous surfaces of the uterus, tubes and ovaries are involved, being limited to the peritoneal lining, without involvement of the uterine muscle or of ovarian tissue. The connective tissues, such as the subcutaneous, and the capsules of the testicle, thyroid and pancreas occasionally show isolated tubercles; parenchymal involvement is absent, however. Rarely, the large intestines and the adrenals

TABLE 6

Tuberculosis of organs in the Macacus rhesus monkey following the intravenous inoculation of virulent human tubercle bacilli

INTRAVENOUS INFECTING DOSE IN MGM. OF VIRULENT HUMAN TUBERCLE BACILLI (GLUCKSON) PER POUND BODY-WEIGHT	MONKEY NUMBER	DURATION OF LIFE IN DAYS AFTER INFECTION	ORGANS				
			Lung	Liver	Spleen	Bone-marrow	Kidney
0.1	1	22	21	41	51	31	11
	2	26	53	11	21	5	21
	3	16	22	0	2p	5p	0
	H 8	22	41	5p	5p	51	1p
	H 9	20	41	4p	5p	5p	0
0.001	4	21	11	51	31	21	0
	5	34	43	11	22	32	11
0.000,01	6	21	22	51	41	31	11
	7	24	21	5p	41	41	11
	H10	58	312	43	55	33	12
	H11	70	59	32	55	1	12
0.000,000,001	H12	101	5	19	18	1	1
	H13	120	0	0	0	0	0

Note: The same markings are used in this table as in table 2, and in addition the "p" sign of table 4.

contain tubercles. In only one of the 26 monkeys did there occur a tuberculosis of the brain; it being a characteristic tuberculoma in the left hemisphere.

The above sites were, however, not common for tuberculous involvement. The lungs, liver, spleen, bone-marrow and kidney are the sites of regular involvement, following the intravenous inoculation of bacilli in the monkey. Of these, the kidney only contains few tubercles regularly, and they are fewer than in the remaining organs. The largest

amount of tuberculosis is confined to the spleen, bone-marrow and liver. It is difficult to determine which of these three organs develops most tuberculosis. The liver of these, however, occasionally escapes macroscopic involvement, especially when large doses of bacilli are used and the period of survival is short. In general, however, irrespective of the grade of the hepatic disease, the individual tubercles in the liver are smaller than those in the remaining organs, regardless of the infecting dose or time interval. The size of the tubercles in the spleen, bone-marrow and kidney is about the same, but they are usually considerably smaller than those in the lung.

The total tuberculosis in the lung is less than that in the liver, spleen and bone-marrow; but in no case was an absence of tuberculosis in the lung noted, a condition which did not prove to be the case for the remaining three organs. Though the number of tubercles found in the lung is less than those found in the spleen, bone-marrow and liver, the size of the individual tubercles in the lung is consistently larger than in any other organ of the body; while in the liver the individual tubercles tend to be the smallest in any of the organs developing the disease after intravenous inoculation.

The lymph nodes draining the various organs and regions of infection become extensively involved in the monkey. It seems that the extreme susceptibility of this animal to tuberculosis to a great extent tends to abolish the differences in susceptibility of the various organs to this disease. In the more resistant animals the differences are more pronounced.

No appreciable difference in the susceptibility of the monkey to human and bovine tubercle bacilli was observed.

The authors appreciate the assistance rendered in the technical parts of this study by Dr. Saul Mebel and Mr. Isadore Soifer.

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Description of Figures

Fig. 1. Characteristic tuberculosis in the organs of the rabbit following the intravenous inoculation of a large dose (1.0 mgm.) of bovine tubercle bacilli after a short interval of time (18 days). Note multiple large miliary tubercles of the lung with slight tuberculosis of the spleen and kidney and complete absence of macroscopic tuberculosis in the liver.

Fig. 2. Characteristic tuberculosis in the organs of the rabbit following the intravenous inoculation of a small dose of bovine tubercle bacilli (0.000,01 mgm.) and simultaneous injection of carbon after a long interval of time (81 days). Note large discrete tubercles of the lung and small miliary tubercles in the spleen, and absence of macroscopic tuberculosis in the liver. (There is a spontaneous interstitial nephritis common in rabbits.)

Fig. 3. Characteristic tuberculosis in a dog following the intravenous inoculation of large doses (0.1 mgm. per pound body-weight) of tubercle bacilli after short intervals of time (47 days). Note miliary tuberculosis of the lung, individual tubercles of moderate size, massive macroscopic tuberculosis of the liver with individual tubercles smaller than those in the lungs, and absence of macroscopic tuberculosis in the spleen and kidneys.

Fig. 4. Characteristic tuberculosis in the dog following the intravenous inoculation of smaller doses (0.001 mgm. per pound body-weight) of bovine tubercle bacilli after long intervals of time (93 days). Note moderate number of discrete tubercles in the lungs with absence of macroscopic tuberculosis in the other organs.

Fig. 5. Characteristic tuberculosis in the monkey following the intravenous inoculation of small doses (0.000,01 mgm.) of human tubercle bacilli after 21 days. Note moderate number of large size tubercles in the lung and miliary tuberculosis of the liver and spleen, with individual tubercles smaller than those in the lung.

Fig. 6. Characteristic tuberculosis in the organs of the monkey after intravenous inoculation of large doses (0.1 mgm.) of virulent human tubercle bacilli after 16 days. Note a complete absence of tuberculosis in the liver (an occasional finding), with a few very small punctate tubercles in the spleen and extensive large miliary tubercles of the lung.

Fig. 7. Characteristic tuberculosis in the guinea pig after the intravenous inoculation of moderate doses (0.001 mgm.) of virulent human tubercle bacilli after short intervals of time (16 days). Note a small number of tubercles in the lung, absence of macroscopic tuberculosis in the liver, and miliary tuberculosis in the spleen.

Fig. 8. Characteristic tuberculosis in the guinea pig after the intravenous inoculation of large doses (0.1 mgm.) of virulent bovine tubercle bacilli after a long interval of time (4 weeks). Note numerous large tubercles in the lung, with questionable tuberculosis in the liver and massive tuberculosis in the spleen, an example of apparent inhibition of extensive pulmonary tuberculosis on the development of liver tuberculosis.

Fig. 9. Characteristic tuberculosis in the guinea pig after the intravenous inoculation of a moderate dose (0.001 mgm.) of virulent bovine tubercle bacilli after a long interval of time (6 weeks). Note a moderate number of large tubercles in the lung, hepatic fibrosis with tendency to healing, and massive tuberculosis of the spleen.

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Description of Figures

Fig. 10. Photomicrograph of a tubercle in the lung of the rabbit, 28 days after the intravenous injection of 0.01 mgm. of living virulent bovine tubercle bacilli. Note size of the tubercle, with large caseous centre.

Fig. 11. Photomicrograph of liver of same animal as in figure 10. Note small size of tubercles and their peripheral distribution in the lobule in conjunction with the portal channels.

Fig. 12. Photomicrograph of spleen of the same animal as in figure 10, showing characteristic tuberculosis of the spleen. Note number and size of tubercles originating primarily in the pulp and occasionally in the Malpighian corpuscles.

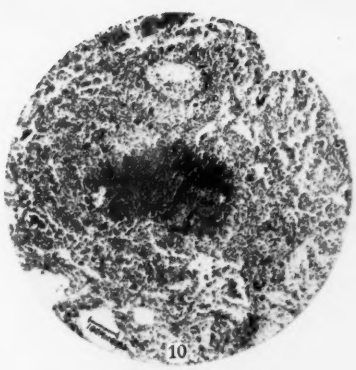
Fig. 13. Photomicrograph of kidney from same rabbit as in figure 10. Note size of tubercle originating at the cortico-medullary boundary from the glomerulus, with round-cell infiltration in the neighboring tissues.

Fig. 14. Photomicrograph of bone-marrow of same rabbit as in figure 10. Two tubercles in the bone marrow.

Fig. 15. Characteristic organic tuberculosis in the dog in response to moderate doses of living virulent tubercle bacilli. Moderate doses (0.01 mgm. per pound body-weight) of living virulent bovine tubercle bacilli (107 days). Note large size of tubercles in lung.

Fig. 16. Liver of dog, same animal as in figure 15. Note massive disease of liver due to numerous small conglomerate tubercles, leaving little intact liver tissue.

Fig. 17. Spleen of dog, same animal as in figure 15. Tuberculosis in the spleen is rare in this animal. Note small single tubercle with moderate doses.



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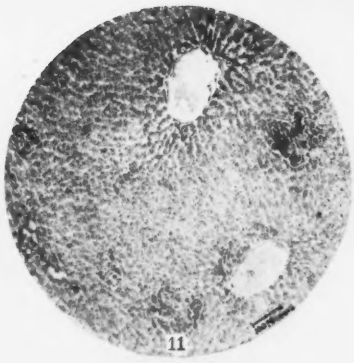

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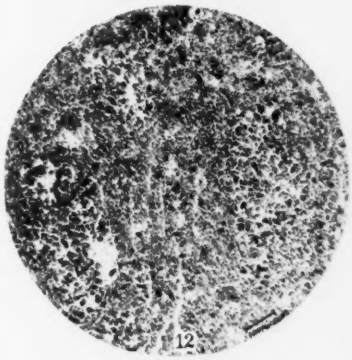

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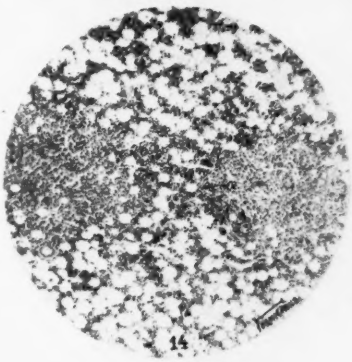

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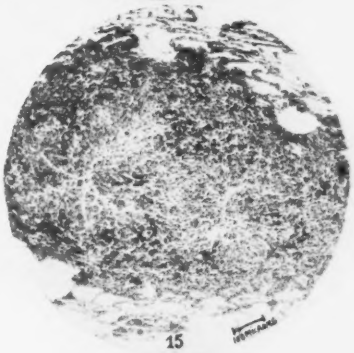

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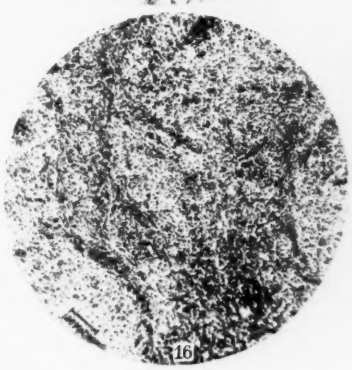

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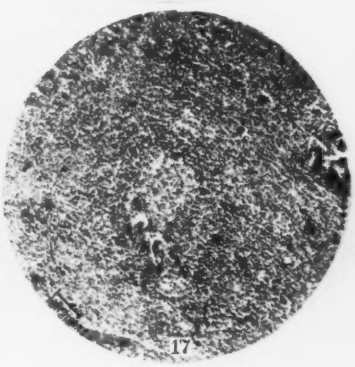

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THE VARIABILITY OF LOCALIZATION OF TUBERCULOSIS IN THE ORGANS OF DIFFERENT ANIMALS[1]

II. THE IMPORTANCE OF THE DISTRIBUTION OF TUBERCLE BACILLI AS CONCERNS DIFFERENCES OF SUSCEPTIBILITY OF THE ORGANS

H. J. CORPER AND MAX B. LURIE

The importance of the localization or deposition of microörganisms in respect to the susceptibility to disease of the different organs in various species of animals and in man, though obvious, was not seriously investigated *from a quantitative standpoint* until after 1920. Prior to that time it was believed by many that the peculiar susceptibility of the lungs of the rabbit to tuberculosis after intravenous inoculations of bacilli was due to a greater localization of the bacilli in the lungs as compared with other organs of the body (1). However Oettinger (2) as early as 1908 had pointed out that after the intravenous inoculation of bacteria (prodigiosus, mouse-typhoid and timothy bacilli) the rabbit's spleen and liver contained many more bacilli than the lungs.

His attempts to evaluate the organic localization of tubercle bacilli after intravenous inoculations into rabbits yielded no significant results, since all his test-reinoculation guinea pigs developed tuberculosis; and it was concluded that the rabbit's lungs, liver and spleen were all heavily seeded with tubercle bacilli after intravenous inoculation.

The first accurate information on the quantitative deposition and subsequent course of particulate matter, intravenously inoculated into various animals, was presented by Drinker, Lund and Shaw (3), (4), (5). Their observations on the dog, rabbit, guinea pig, cat, rat, chicken and turtle demonstrated that particles no larger than one micron were deposited, to a great extent, in the liver of all the animals except the cat. In rabbits, after one hour, the lungs contained 1.6 and the liver 88.2 per cent of the particulate matter, while after sixteen hours the relation still held in that the lung contained 0.6 and the liver 32.4 per cent.

There are many observations on record, to show that when india ink was used intravenously and its organic distribution was noted with the

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naked eye (6) or microscopically (7), there resulted a greater deposition in the liver and spleen than in the lungs, but the accuracy of such observations has not been beyond criticism.

The present studies were undertaken in order to determine, as precisely as possible, the quantitative deposition of tubercle bacilli in the various organs of several animal species after intravenous inoculation. In the early part of the study tubercle bacilli themselves were used, but this procedure was abandoned as not being sufficiently accurate, if indeed it was at all feasible. India ink is a fine suspension of particulate material. Its carbon, which is insoluble and practically inert, or only slightly irritating to tissues, is of about the same dimensions as microörganisms, possesses a distinct color, and is therefore susceptible of fairly accurate determination. It was accordingly chosen to serve as an indicator of the distribution and deposition of tubercle bacilli to the various organs. It was, however, first necessary to determine how far the distribution and deposition of the carbon particles corresponded to those of tubercle bacilli. The studies with carbon were pursued both microscopically and chemically. In order to lessen the huge task of detailed microscopic study of all the animals to be used, only the rabbit was selected for this purpose, because the contrast of the various organs as regards susceptibility is greater in the rabbit than in the other animals concerned.

When india ink is introduced into the circulation of rabbits the carbon is deposited, according to the amount per gram of tissue, chiefly in the spleen, liver, lungs, bone-marrow and kidneys. The remaining organs show no appreciable amount of carbon, when investigated by a delicate quantitative method. The organs which exhibit the greatest deposits of carbon are the spleen and liver; and in these organs are located the reticulo-endothelial cells of Aschoff and Kiyono. In the spleen the particles of carbon are phagocytosed by (1) the macrophages, those large mononuclear and highly phagocytic cells which engulf altered red-blood cells; (2) the endothelial cells lining the sinuses of the spleen; and (3) the reticular cells of the pulp and, to a lesser degree, those of the corpuscles. The polymorphonuclear leucocytes, and the unaltered lymphocytes do not phagocytose the carbon. Consequently, the carbon is located primarily in the pulp, while the Malpighian corpuscles are relatively free from it. In the splenic pulp phagocytic cells are much more numerous, within a given area, than within a similar microscopic field of any other organ. Though tubercles may occasionally develop in the

corpuscles of the spleen, by far the greater number of tubercles are found in the pulp of this organ, corresponding to the location of the major deposits of carbon.

If an animal which received india ink intravenously is killed immediately after inoculation the liver lobules are marked out by the inflowing carbon in the hepatic-artery capillaries as these course from the periphery to the centre of the lobule. This circulatory arrangement is an important factor in the distribution of the phagocytosed carbon in the liver lobules. For several days following intravenous inoculation the carbon is seen to be mostly deposited in the periphery of the lobule, while the central portion contains less. Carbon is present in the Kupffer cells of the sinusoids of the liver, and those which first come in contact with the inflowing particles phagocytose more than do those situated nearer the centre of the lobule. Tubercle in the liver originates primarily from the Kupffer cells in the sinusoids in all the animal species studied. Later the Kupffer cells, which have become filled with carbon particles, are often detached from the sinusoidal walls, have their processes drawn in, and become free in the sinusoidal circulation. From there they enter the general circulation, or the lymph spaces surrounding the portal canals. Frequently, carbon-laden cells are seen in the periportal lymph spaces. These may either be detached Kupffer cells, which have wandered into these spaces, or they may be the original clasmatocytes which are present in the connective tissue in the portal canals. As happens with the distribution of carbon, the tubercles which develop after the intravenous inoculation of tubercle bacilli are mainly located in the periphery of the lobule. In some animals they form a circle about the lobule, with the central portion relatively free from tubercle. Tubercles also originate to a lesser extent from the connective tissues in the portal canals, presumably either from sessile histiocytes or from emigrated loosened Kupffer cells which have localized in the lymph spaces.

In the rabbit there occurs quite a deposition, relatively speaking, of carbon in the lung. It was not clearly determined what cell or cells in the lung phagocytose carbon to the greatest extent; whether it is the endothelial cells of the capillaries alone, or the histiocytic elements of the alveolar walls alone, or both. Free cells, laden with carbon particles, are often seen in the alveolar spaces, but their origin has not been determined. In general, however, it was found that the cells which are laden with carbon or phagocytose it are also responsible for tubercle formation.

In the bone-marrow the carbon is engulfed by the endothelial cells of the sinuses and by the reticular cells of the parenchyma; the remaining cells of the bone-marrow fail to take up any carbon.

Little carbon is deposited in the kidney, where it is found either in the endothelial cells of the glomeruli or the endothelial cells of the capillaries about the convoluted tubules. No appreciable amount of carbon is deposited in the medulla, and tubercles rarely originate in it. The chief site of tubercle-formation is the cortex of the kidney, in the glomeruli or in the capillaries between the convoluted tubules.

Tuberculosis, therefore, occurs only in those organs where the localization of carbon is appreciable, while those organs which fail to store carbon in noticeable amount fail to develop perceptible tuberculosis. Thus, tuberculosis in the rabbit, after intravenous inoculation, is limited chiefly to the lung, spleen, kidney, bone-marrow and liver, which are also the organs of greatest localization of carbon, the remaining organs escaping involvement. Furthermore, in the rabbit, with the exception of the lung and liver in which certain other factors must play a rôle, the number of tubercles in a given organ is in direct ratio to the amount of carbon stored. Thus, if the organs of the rabbit are arranged in the order of the number of tubercles developed within a given area, they rank as follows: spleen, bone-marrow and, finally, kidney. This sequence is also the order of storage of carbon in these organs, for the greatest amount is present in the spleen and next in the bone-marrow, while the smallest amount is in the kidney. Finally, tubercle-formation occurs in those parts of given organs where carbon particles localize to the greatest extent.

To correlate further the distribution of carbon particles and tubercle bacilli, a series of rabbits was inoculated simultaneously with suspensions of different doses of living tubercle bacilli and of Higgins water-proof india ink. Microscopic sections were stained with hematoxylin and eosin, and for tubercle bacilli. The epithelioid cells of the tubercles in all the organs contained particles of carbon, and tubercle bacilli were seen in these carbon-laden epithelioid cells. It thus becomes apparent that the cells which take up carbon particles are identical with those which phagocytose tubercle bacilli.

In this experiment only a single inoculation of carbon was given; and in the lung the majority of the older tubercles contained carbon particles, while the epithelioid cells of the younger tubercles were free from them, since the multiplication of these cells resulted in a dispersion of the car-

bon. In the rabbit's lung tubercle originates from the cells of the adventitia of the blood-vessels; these cells are frequently laden with carbon. It is common to find the lumina of the smaller blood-vessels gradually becoming obliterated by the multiplication of pericytes heavily laden with carbon. The cells of the endothelial lining of these vessels do not contain carbon particles, and play no rôle in the formation of tubercle. The cell responsible for the origin of the tubercle in the alveolar walls was not determined, but, irrespective of the cell of origin, the epithelioid cells of these tubercles contained carbon particles. Similarly, the areas of exudative tuberculosis, in which the alveoli were completely filled with cells which morphologically resembled the monocytes of Sabin (8) and Cunningham (9), also contained particles of carbon. The significant fact derived from this experiment was that the epithelioid cells of the tubercles, regardless of their origin, contained carbon particles, so that the identity of the cells phagocytosing tubercle bacilli and carbon particles seems to be established for the lung.

In the rabbit's liver the epithelioid cells of tubercles are heavily laden with carbon. No tubercles are found in which the epithelioid cells do not contain particles of it. In explanation of this, it may be considered that the Kupffer cells, from which hepatic tubercle originates, carry much carbon; and, since the rate of tubercle-formation in the rabbit's liver is very slow, it follows that the division of the original Kupffer cells, which had picked up tubercle bacilli and carbon particles, has not occurred to so great an extent as in the case of tubercles of the lung. The same epithelioid cells of hepatic tubercles also contained tubercle bacilli and carbon particles at the same time. Commonly, these tubercles consisted of a single large giant cell, always containing carbon particles, distributed about the *cytocentrum* in the form of a hollow sphere; cells which Foot (10) has designated as *ring cells* and which correspond exactly to cells described by Maximow (11) in his recent studies on tuberculosis in tissue cultures. The sinusoids often contained detached cells, bearing both carbon and tubercle bacilli. Similar free cells, containing both elements, are to be seen in the sinuses of the spleen. In the rabbit's liver there is a marked tendency toward healing. The fibroblasts contain carbon particles in their cytoplasm, a circumstance which indicates their derivation from epithelioid cells. In rabbits inoculated with both living tubercle bacilli and carbon particles simultaneously, just as in rabbits, guinea pigs and dogs inoculated with living tubercle bacilli alone, the site for the greatest amount of tuberculosis is in

the periphery of the lobule in immediate proximity to the portal canals, whereas the central portion of the lobule is relatively free from the disease, in accordance with the distribution of carbon to the liver.

The spleen of rabbits, inoculated with tubercle bacilli and india ink at the same time, shows characteristic tubercle-formation, in which giant cells of the Langhans type are prominent. The epithelioid cells, as well as the giant cells, of these tubercles are heavily laden with carbon particles. At the periphery the epithelioid cells contain more carbon than do those in the central portions of the tubercle. As long as the epithelioids are intact the carbon is limited to the cytoplasm of the cells as more or less fine granules. These cells may contain so much carbon as to completely blot out the structure of the cell. When giant cells occur the carbon is distributed to form a hollow sphere about the *cytocentrum*, as was found by Maximow in tissue culture. These "ring cells" are also seen in the lung and bone-marrow, as well as in the spleen and liver. When necrosis occurs and the cell-membranes disappear the carbon is found diffusely and irregularly scattered as minute granules or particles in the necrotic tissue.

The tubercles in the spleen are found in greater numbers in the pulp than in the corpuscles. The epithelioid cells of the tubercles in the pulp are more closely packed together, contain less cytoplasm and are more heavily laden with carbon particles than those occurring in the corpuscles. These facts are in accord with the distribution of carbon to these two portions of the spleen; that is, the corpuscles arrest fewer particles of carbon, and hence fewer tubercle bacilli than the pulp, again indicating that the cells which take up carbon particles and tubercle bacilli are identical. The epithelioid cells of the tubercles of the pulp often contain altered red blood-cells or hemoglobin pigment as well as carbon. The epithelioid cells of the tubercles in the spleen, to a lesser degree in the bone-marrow, and to a slight degree in the liver, contain hemoglobin pigment and altered red blood-cells, indicating the identity of the cell which phagocytoses tubercle bacilli, carbon particles and injured red blood-cells, and making it probable that the macrophage of the spleen or the splenocyte of Aschoff plays a prominent rôle in the genesis of tubercle in the rabbit and also in the guinea pig and dog.

The bone-marrow of the rabbit, inoculated simultaneously with living bovine tubercle bacilli and india ink, also discloses the unity of the cell instrumental in the phagocytosis of carbon and the formation of tubercle. The epithelioid and giant cells of all tubercles developing in the bone-

marrow contain carbon particles, and the disposition of these particles is essentially identical with that described for the spleen. Tubercle bacilli and carbon particles are demonstrable in the same cells. The individual features in the bone-marrow are that tubercle formation is more common in the peripheral portion which is nearest the bone than in the central portion, which can be correlated with the fact that the parenchymatous portion of the bone-marrow is primarily located at the periphery, while the central portion of the bone-marrow consists mostly of fat cells, with only relatively few islands of parenchyma. It is in the parenchyma where the endothelial cells of the sinuses and the reticular cells, which support the various cell-elements of the bone-marrow, are found in greatest number, and it is in these that the carbon is chiefly localized and where tubercles chiefly occur.

In the bone-marrow the tubercles commonly enclose large spaces free from fat cells but with their remains enmeshed. When necrosis occurs, these rounded spaces coalesce, and diffusely deposited carbon particles are seen in the necrotic tissue. In explanation of the presence of these fat globules in the tubercles, when they are absent from the normal parenchyma, it is assumed that the tuberculous process causes an absorption from the fat depots of the body, and that, while the lipoid of the fat cells of the bone-marrow which are in free communication with the circulation become absorbed, the fat cells enmeshed in a tubercle, because of the latter's avascularity, are not deprived of their fat.

Since the kidney of the rabbit arrests but little carbon, after a single intravenous inoculation of living tubercle bacilli and india ink the epithelioid cells of the old tubercles were found to contain only a small amount of it, and, as in many tubercles in the lung, the epithelioid cells may not contain any carbon particles. Since only a single injection of carbon was given and the epithelioid cells continue to divide and multiply, it is self-evident that the original store of carbon particles is soon exhausted. In the kidney some epithelioid cells are found which contain both carbon particles and tubercle bacilli.

In a subsequent paper of this series it will be shown that, when dead tubercle bacilli and india ink are injected into rabbits, dogs and guinea pigs, the epithelioid cells of the tubercles are laden with carbon particles.

Animals with spontaneous anthracosis of the lung, and given living or dead tubercle bacilli intravenously, often exhibit carbon particles in the epithelioid cells of the resulting pulmonary tubercles, indicating further that the cells which phagocytose inhaled carbon particles can phagocytose tubercle bacilli inoculated intravenously.

In reviewing the data presented thus far in Studies I and II, it is clear that only those organs will develop tuberculosis, following the intravenous inoculation of tubercle bacilli, which will also show a significant amount of carbon after intravenous injection. Even the monkey, which is extremely susceptible to tuberculosis and in which tuberculosis occasionally develops in almost every organ in the body, reveals the disease regularly only in the spleen, bone-marrow, liver, lung and kidney, the chief sites of deposition of carbon, while all the remaining organs usually escape the disease.

Again, tuberculosis develops to the greatest extent in those parts of the organs which are the sites of greatest storage of the carbon. Thus, tubercle in the lung originates primarily from some element in the alveolar walls and capillaries, and tubercles in the liver develop primarily at the periphery of the lobule after the intravenous inoculation of living bacilli, while the central portion of the lobule remains relatively free from tuberculosis. In the spleen most tubercles develop in the pulp, and only a few in the corpuscles. In the bone-marrow the tubercles occur mainly in that portion which is in close proximity to the bone, while the central portion contains much less tuberculosis. In the kidney most tubercles originate in the cortex from the glomerulus or from the capillaries in the convoluted tubules, while the medulla is far less often the seat of tuberculous involvement.

Finally, after the coincident injection of both living or dead tubercle bacilli and india ink, the epithelioid cells of all the tubercles in the different organs contain both carbon particles and tubercle bacilli.

From the evidence presented thus far, it seems justifiable to conclude that, whatever may be the cell of origin of tubercle, in the different organs the cells which phagocytose tubercle bacilli and carbon particles are identical, and that, if the relative amount of carbon stored by these cells after the introduction of india ink into the circulation be determined, this will serve as an index of the number of tubercle bacilli deposited under like conditions.

THE QUANTITATIVE DEPOSITION OF CARBON (INDIA INK) IN THE VARIOUS ORGANS OF RABBITS, GUINEA PIGS, DOGS AND MONKEYS, AND THE RÔLE OF THE DISTRIBUTION OF THE BACILLI IN TUBERCULOSIS OF THE ORGANS

Having established in the foregoing study that india ink can serve as an index of the distribution of tubercle bacilli to the different organs, the

actual quantitative determination of the carbon deposited in each organ can be proceeded with, and the data obtained will serve for the purpose of drawing conclusions regarding the distribution of tubercle bacilli to these organs following intravenous inoculation.

Method of Determination of Carbon in Tissues

A weighed amount of tissue is placed in a test-tube and covered with 40 per cent potassium hydroxide; and the tube is put in a boiling water-bath until the tissue is completely digested, which requires about 10 to 20 minutes in the case of lung tissue. After cooling, an equal volume of 95 per cent alcohol is added, the mixture is well shaken, and then centrifugated at high speed for at least 15 minutes, when the carbon from the tissues settles to the bottom of the tube, almost free from admixture with solid nondigested tissues. Occasionally with liver, kidney and bone-marrow, tissues containing large quantities of fat, prolonged boiling results in a saponification of the fats, and when alcohol is added soaps are precipitated, but these can be redissolved with concentrated hydrochloric acid. The supernatant alcohol is poured off, and the centrifugate is washed twice with ether to extract any fatty substances further. The final washed carbon is suspended in saline solution by thorough trituration with the saline solution added drop by drop. There results a very good suspension of the carbon particles, which remains for longer than a week. The chief error of the method lies in an occasional lack of fine subdivision of the particles, when accurate analysis becomes difficult. The unknown suspension of carbon obtained from the tissues is compared with a known dilution of the original india ink made in saline solution. The two suspensions were compared in a Klett colorimeter-nephelometer, and the amount of carbon figured from the readings obtained. With the total weight of the organ known and the content of the sample analyzed, the amount of india ink per gram of tissue can be determined.

With amounts of tissue (liver, spleen, lung and kidney) from 1.5 to 5 gm., the method of analysis described above has an error of less than 10 per cent, usually less carbon being found, so that in no case was more carbon obtained than that added to the test.

The Relative Distribution of Carbon in Different Organs of the Rabbit after the Intravenous Injection of India Ink

A series of 27 rabbits were given 3 cc. of a 1 to 3 dilution in saline solution of Higgins *Eternal* black india ink per pound of body-weight, which

TABLE 1

The relative distribution of macroscopic tuberculosis and carbon in the organs of rabbits at intervals, after the coincident intravenous inoculation of india ink and virulent bovine tubercle bacilli

AMOUNT OF TUBERCLE BACILLI AND INDIA INK GIVEN INTRAVENOUSLY	RABBIT NUMBER	INTERVAL IN DAYS	LUNGS		LIVER		SPLEEN		KIDNEYS	
			Tuber-culosis	India ink	Tuber-culosis	India ink	Tuber-culosis	India ink	Tuber-culosis	India ink
0.1 mgm. tubercle per pound body-weight + 1 cc. india ink per pound body-weight.	1 to 6	12 to 20	4p*	+++†	0	+++	2p	++++	0	+
0.01 mgm. tubercle per pound body-weight + 1 cc. india ink per pound body-weight	1 and 2	12 and 13	0	++	0	+++	0	++++	0	+
	3 to 7	20 to 26	51	++	0	+++	21	++++	0	+
0.001 mgm. tubercle per pound body-weight + 1 cc. india ink per pound body-weight.	1 to 4	22 to 29	51	++	0	+++	21	++++	0	+
	5	43	32	+	0	+++	0	++++	0	+
0.000,01 mgm. tubercle per pound body-weight + 1 cc. india ink per pound body-weight.	1 and 2	38	22	+	0	+++	21	++++	0	0
	3 to 7	43 to 76	34	+	11	+++	22	++++	12	0

* These markings are in accord with those given for table 2, study I. The number of tubercles is indicated by the left integer from 1 = a few tubercles to 5 = massive disease, while the size of the tubercles in millimetres is indicated by the right integer, "p" indicating that the tubercles are only a fraction of a millimetre in size. Where the variations as a whole were not greater than one point in the different animals tabulated, the average figure alone is given for all of them given the same amount of bacilli and india ink.

† The markings 0 to ++++ indicate the approximate darkening of the organ, as determined by naked-eye appearances, due to the presence of the india ink, and is obviously only a very crude designation.

is a relatively coarse suspension of carbon particles in water. These animals were divided into groups of four, and were killed after the following intervals after injection: 30 minutes, 3 hours, 1, 4, 7 and 12 days, and one month. There are individual variations, but with the exception of the 30-minute interval a more or less constant relation is revealed between the amounts of carbon deposited in each organ. In all cases and after all intervals the spleen stores the greatest amount of carbon per gram of tissue as compared with the other organs of the same rabbit. The liver stores less carbon than does the spleen but more than the lung

TABLE 2

*The quantitative deposition of carbon in the different organs of the rabbit after the intravenous injection of finely divided india ink.**

TIME INTERVAL	RABBIT NUMBER	AMOUNT OF CARBON IN CUBIC CENTIMETRES OF THE ORIGINAL INDIA INK PER GRAM OF TISSUE						
		Lung		Liver		Spleen		Bone-marrow
		Cubic centimetre of ink per gram of tissue recovered	Per cent of total carbon injected	Cubic centimetre of ink per gram of tissue recovered	Per cent of total carbon injected	Cubic centimetre of ink per gram of tissue recovered	Per cent of total carbon injected	Cubic centimetre of ink per gram of tissue recovered
Immediately afterward	1	0.06		0.03		0.03		trace
days								
1	2 to 6	0.021	5	0.028	38.7	0.09	4.4	trace
5	7	0.01		0.02		0.05		trace
8	8	0.01		0.02		0.12		trace
	9	0.006		0.01		0.06		trace
21	10	0.006		0.02		0.05		trace

*Three cubic centimetres of a 1 to 3 dilution of Higgins *Waterproof* india ink in physiological saline solution was given per pound body-weight.

of the same animal. The only interval at which the lung contains more carbon than the liver is the 30-minute period. This is probably accounted for in that the lung is the first capillary region to which the carbon is carried after intravenous injection, and some time is necessary for the circulating blood to flush the carbon through the pulmonary capillaries and carry them to their ultimate depots. Three hours after injection of the india ink the deposition of the carbon in the different organs is relatively the same as it is at all subsequent intervals. Although only a few observations are recorded on the bone-marrow, it was found that a

significant quantity of carbon is deposited here. In the kidneys of the rabbit the amount of carbon is small—less than that in the lung, liver and spleen.

One month after the intravenous injection of the india ink the actual amount of carbon present in the lung, liver and spleen is less than after shorter intervals, but the relative amounts present in each organ tend to be proportionately the same, so that the lung still contains the least carbon, the liver more, and the spleen the largest amount per gram of tissue. Regardless of the factors controlling the distribution of the carbon, the relative amounts deposited and present in each organ does not change even after an interval of one month.

Since the state of division of the particles of carbon might possibly influence the distribution of india ink to the different organs, a number of

TABLE 3

*The quantitative deposition of carbon in different organs of the rabbit following intraarterial (Carotid) injection of 3 cc. of finely divided india ink**

INTERVAL	RABBIT NUMBER	AMOUNT OF CARBON IN CUBIC CENTIMETRES OF THE ORIGINAL INDIA INK PER GRAM OF TISSUE				
		Lung	Liver	Spleen	Kidney	Bone-marrow
3 days	1	0.007	0.006	0.02	trace	trace
	2	0.004	0.01	0.02	trace	trace
3 weeks	3	0.004	0.02	0.03	trace	0.01

* Three cubic centimeters of a 1 to 3 dilution of Higgins *Waterproof* india ink in physiological saline solution was given per pound body-weight.

rabbits were injected with Higgins *Waterproof* india ink, which is a finer and more uniform suspension of carbon particles than Higgins *Eternal* black india ink. The results of these analyses are given in table 2. It is noted upon examining table 2 that there is no essential difference between the relative distribution of the fine or the coarse suspension of carbon particles to the different organs. In this case also the largest amount of carbon is deposited in the spleen, next the liver, then the lung, then the bone-marrow, and least in the kidney; and the relative distribution to the different organs was not affected by the interval of time elapsing between the injection of the carbon and the examination of the animal. It was found that the entire lung stores about 5 per cent of the total quantity of carbon injected, and the liver 38.7 per cent, while the spleen contained 4.4 per cent of the total amount of carbon 24 hours

after injection. It is apparent from these analyses that the size of the carbon particles and of tubercle bacilli, provided these are not large enough to plug the capillaries, is of no significance in their distribution to the different organs.

The organs of rabbits were also analyzed after the intraärterial injection of india ink; and the results, recorded in table 3, indicate that there is no difference in the relative deposition in the different organs from that following intravenous injection.

In summary, therefore, the distribution of carbon particles, and therefore of tubercle bacilli, considered as inert non-multiplying particulate matter, to the different organs of the rabbit, after intravenous or intra-arterial inoculation, places these organs in the following sequence according to the amount of carbon deposited per gram weight of tissue: spleen, liver, lungs, the bone-marrow, and kidney. The relative amount of carbon deposited in these organs does not change for intervals from three hours to one month after the injection of india ink.

If the distribution of tubercle bacilli to the organs alone were the controlling factor in organic tuberculosis in the rabbit, the greatest amount of the disease should be found in the spleen of this animal, the liver following, then the lung, next the bone-marrow, and the kidney should be least involved. However, this is not the case. In spite of the fact that fewer bacilli are deposited in the lung than in the spleen or the liver the lung develops much more tuberculosis than the two latter organs. In addition, even though far more bacilli are deposited in the liver than in the kidney, the latter is the seat of more involvement. Therefore, in the case of the lung and the liver, standing in opposition regarding the development of the disease, other factors than the distribution of bacilli to these organs must be instrumental in determining the amount of tuberculosis developed in them. That the distribution of carbon, however, is a significant factor in the rabbit is evident from the fact that of the remaining three organs studied the spleen develops the most tuberculosis, the bone-marrow develops an intermediate amount and the kidney develops the least, which is in accord with the distribution of carbon particles and tubercle bacilli to these organs. It may be assumed from this that in the lung there is a factor other than the deposition of bacilli favoring the development of the disease, while in the liver there exists an inhibitory factor on the other hand.

The Distribution of Carbon in Different Organs of the Guinea Pig after the Intravenous Injection of India Ink

A large series of guinea pigs was given intravenous injections of india ink, and the different organs were analyzed after definite intervals, the results of which analyses are recorded in table 4. These reveal essentially the same relative distribution of carbon to the various organs as was noted for the rabbit, in that the largest deposit of carbon per gram of tissue occurs in the spleen, the deposit in the liver is about half that in the spleen, that in the lung is much less, and the kidney usually contains

TABLE 4

*The quantitative deposition of carbon in different organs of guinea pigs following the intravenous injection of india ink in fine suspension**

TIME INTERVAL AFTER INJECTION	AMOUNT OF CARBON IN CUBIC CENTIMETRES OF THE ORIGINAL INDIA INK PER GRAM OF TISSUE†		
	Lung	Liver	Spleen
30 minutes	0.002	0.02	0.015
3 hours	0.001	0.013	0.038
1 day	0.0	0.01	0.03
2 days	0.005	0.021	0.035
3 days	0.008	0.013	—
9 days	0.002	0.01	0.012
15 days	0.007	0.01	0.02
16 days	0.005	0.02	0.02
19 days	0.007	0.02	0.01
7 months	0.007	0.01	0.005
8 months	0.002	0.005	0.01

* Four cubic centimetres of a 1 to 6 dilution in physiological saline solution of Higgins *Waterproof* india ink was given per pound body-weight.

† The kidney contained only a trace of carbon, which could not be accurately determined.

no carbon detectable by our method of analysis. India ink (Higgins *Eternal*), containing coarse suspensions of carbon which were tolerated intravenously with no injurious effect in the rabbit and dog, invariably killed the guinea pig, even if a 1 to 6 saline-solution dilution was used. Suspensions of the finer carbon (Higgins *Waterproof* india ink) were tolerated intravenously in a dilution of 1 to 5 with physiological salt solution. There was no fundamental difference in the ratio of the distribution of carbon to the different organs even after eight months, as compared with three hours after injection, although the actual quantity of carbon in each organ tended to diminish with time. Eight months

afterward the spleen still contained the greatest amount of carbon, with the liver, lungs and kidneys following in order.

There is, however, one difference of fundamental importance between the rabbit and the guinea pig. This is that although in these two animals the lung contains less deposited carbon than does the spleen or liver, the guinea pig's lung contains much less carbon than does that of the rabbit. The same difference as regards tubercle bacilli was noted earlier by Krause (12) whose conclusions were drawn from anatomical, histological and reinoculation observations. Krause observed that one factor in the relative freedom of the guinea pig's lung from tuberculous involvement, as compared with the massive involvement of the rabbit's lung, may be the greater deposition of tubercle bacilli in the lung of the rabbit as compared to the guinea pig, but especially a greater *early* fixation of bacilli in the rabbit's lung. As Krause points out, the deposition of bacilli in the lung of the guinea pig is not the only factor in the development of tuberculosis there. This also appears to be certain from our experiments, for during the first four weeks following the intravenous inoculation of tubercle bacilli, the pulmonary disease in this animal exceeds the hepatic disease, even though the liver contains many more tubercle bacilli originally.

Krause considers intrapulmonary differences of lymphatic tissue, blood supply and lymph flow decisive in determining the characteristic differences of pulmonary involvement in the rabbit and guinea pig. Whatever the dose of tubercle bacilli inoculated, he would presume that, relatively, the same ratio of tubercle bacilli would be brought to the lungs of both animals. But the amount of pulmonary tuberculosis that resulted would be contingent on the numbers of bacilli that remained fixed in the lung. Anatomically and physiologically, the rabbit's lung, according to Krause, favors the more or less permanent arrest of particles (bacilli) brought to it by the blood-vessels or the air-passages, while that of the guinea pig promotes the further lymphatic transit of particles to the tracheobronchial lymph nodes. Therefore, in Krause's opinion, relatively small doses of tubercle bacilli, whether inhaled or embolized in the intrapulmonary circulation, should set up much less early disease within the guinea pig's lung than in the rabbit's. But large or excessive doses, similarly received, should give rise to relatively much pulmonary tuberculosis also in the guinea pig, simply because the drainage or "cleansing" capacity of the animal's lung would be soon overtaxed; and the bacilli would remain arrested within the lung, instead

of being carried on to the tracheobronchial lymph nodes, as happens when the animal's lymphatic apparatus is functioning normally and efficiently.

On the other hand, in the guinea pig the spleen contains the greatest amount of carbon deposited after intravenous injection, and it is also the seat of most tuberculous involvement following the intravenous inoculation of tubercle bacilli. The susceptibility of the spleen to tuberculosis in this case is self-evident, at least in part, accounted for by the greater deposition of the tubercle bacilli. Krause considers the exceptionally high content of lymphoid tissue (Malpighian bodies), normal for the guinea pig, also a factor in this connection.

The kidney of the guinea pig rarely develops tubercles macroscopically, while in the rabbit renal tuberculosis is fairly common, especially that due to bovine bacilli. This difference in susceptibility between the kidney of the guinea pig and the rabbit is also satisfactorily explained as due to the deposition of the bacilli.

In the guinea pig the rôle of the distribution of bacilli after intravenous injection is evidently significant.

The Quantitative Distribution of Carbon to Different Organs of the Dogs after the Intravenous Injection of India Ink

Two series of dogs were given intravenous injections of india ink, 12 adult dogs being given 1 cc. of the coarse suspension, Higgins *Eternal* black india ink, as a 1 to 1 dilution in physiological salt solution per pound body-weight. Another series of 10 young dogs were given the same quantity of the fine suspension, Higgins *Waterproof* india ink. These dogs were killed at different intervals, and the organs were analyzed for their carbon content. The first series gave unsatisfactory results in the lung, since adult city dogs have spontaneous anthracosis, and the added carbon made quantitative determinations impossible.

The series of young dogs, which were without spontaneous anthracosis, yielded constant and valuable findings. The results of the quantitative determinations of carbon for the different organs are recorded in table 5. The distribution of carbon is essentially the same as that noted for the rabbit and guinea pig, in that the spleen receives the greatest amount of carbon per gram of tissue, the liver considerably less, the lung containing about half as much as the liver, the bone-marrow less than the lung, and the kidney only a trace. Of the total carbon the entire lung of the dog contained about 5 per cent, an equal amount being found in the spleen,

while the liver received about 50 per cent. No appreciable alteration in the proportion of carbon deposited in the different organs was noted after different intervals of time.

If the deposition of the carbon in the different organs is an index of the distribution of bacilli, which is unquestionably the case, the organic susceptibility of the dog to tuberculosis cannot be explained on the basis

TABLE 5

*The quantitative deposition of carbon in different organs of young dogs after different intervals of time, following the intravenous injection of fine suspensions of india ink**

TIME INTERVAL	NUMBER OF DOG	AMOUNT OF CARBON IN THE DIFFERENT ORGANS							
		Lung		Liver		Spleen		Kidney	Bone-marrow
		Cubic centimetre of ink per gram of tissue recovered†	Per cent of total carbon injected	Cubic centimetre of ink per gram of tissue recovered	Per cent of total carbon injected	Cubic centimetre of ink per gram of tissue recovered	Per cent of total carbon injected	Cubic centimetre of ink per gram of tissue recovered	Cubic centimetre of ink per gram of tissue recovered
1 day	62, 63, 64	0.008	5.2	0.027	54.7	0.037	4.5	0.004	0.005
5 days	61, 65, 66	0.16	6.7	0.023	38.7	0.049	7.0	0.003	0.007
6 days	70	0.009	5.5	0.024	41.2	0.008	0.9	trace	
7 days	67	0.006	2.7	0.021	48.2	0.043	5.2	trace	0.005
11 days	68 and 69	0.010	3.8	0.032	51.6	0.036	4.7	trace	0.005
Average of all intervals		0.010	5.3	0.025	50.3	0.038	5.2	trace	0.006

* The dogs were given intravenously 2 cc. of a 1 to 1 dilution in physiological saline solution of Higgins *Waterproof* india ink per pound body-weight.

† These figures indicate the cubic centimetres of undiluted original india ink recovered per gram of tissue.

Each figure on the amount of carbon present per gram of tissue for each organ except the bone-marrow is the mean of two separate specimens of tissue.

of the deposition of the tubercle bacilli in these organs. Thus, the spleen, which receives the greatest amount of bacilli, usually escapes tuberculosis completely after intravenous inoculation of moderate doses of tubercle bacilli, while the liver, where the deposition of carbon is much less, develops so massive a tuberculous involvement that little normal parenchyma remains.

In the dog, after intravenous inoculation of small doses of tubercle bacilli, the lung is the only organ where tuberculosis develops macro-

scopically, in spite of the fact that there are fewer bacilli deposited in the lung than in the spleen or liver per gram tissue. That the deposition of the bacilli in the various organs is a factor in the development of tuberculosis in the dog is apparent from the fact that the liver, after moderate doses of bacilli, exhibits more tubercles than does the lung, as well as the fact that the bone-marrow develops more tubercles than does the kidney.

The kidney of the dog displays less tuberculosis than does the kidney of the rabbit, but more than the kidney of the guinea pig, which is in accord with the relative distribution of carbon to the kidneys of these three species of animals. There is more carbon deposited in the kidney of the rabbit following intravenous injection than in the dog's kidney, while no appreciable carbon is deposited in the kidney of the guinea pig.

It was pointed out in the case of the rabbit, an animal with a marked resistance toward human-bacillus tuberculosis, that the rôle of the distribution of bacilli is of less importance in the development of disease of the various organs than it is in more susceptible species; and so it is with the dog, also an animal of greater resistance.

The Quantitative Deposition of Carbon in Different Organs of the Monkey after the Intravenous Injection of India Ink

Six *Macacus rhesus* monkeys were given femoral-vein injections of 4 cc. of a 1 to 4 dilution in saline solution of Higgins *Waterproof* india ink per pound body-weight. The animals were divided into three groups of two each. The first group was killed 24 hours after injection, and the second two weeks and the third two months after injection. The different organs were analyzed for carbon, and the results are recorded in table 6. In the monkey, as in all the other species studied, the chief deposition of carbon is in those organs where the reticulo-endothelial cells are found in greatest abundance. The greatest quantity of carbon per gram of tissue is deposited in the spleen, and considerably less in the liver, while in the lung there is to be found a good deal less carbon (one-third to one-fifth) than in the liver. In the monkey the amount of carbon in the bone-marrow is somewhat greater than that in the lung, while in the dog and rabbit more carbon is deposited in the lung than in the bone-marrow. There appears to be no essential difference in the relative amount of carbon contained in the different organs of the monkey at different

intervals of time up to 2 months after injection. Nearly all of the monkey's organs and tissues may be involved after the inoculation of large amounts of living tubercle bacilli, but in the majority of cases the disease occurs regularly only in the five organs where there is an appreciable deposition of the tubercle bacilli. Of these five organs, the kidney is least involved, which coincides with the relative amount of bacilli deposited in this organ. The lung usually develops fewer tubercles than do the remaining three organs, which is in direct accord with the deposition of tubercle bacilli. Of the remaining three organs the spleen develops the most tuberculosis, it being also the site of the deposition of most tubercle bacilli. The bone-marrow shows less tuberculosis than

TABLE 6

*The quantitative deposition of carbon in the different organs of Macacus rhesus monkeys after intravenous (femoral) injection of a fine suspension of india ink**

TIME INTERVAL AFTER INJECTION	MONKEY	AMOUNT OF CARBON IN CUBIC CENTIMETRES OF ORIGINAL INDIA INK PER GRAM OF TISSUE				
		Lung	Liver	Spleen	Kidney	Bone-marrow
1 day	C5 and C6	0.008†	0.031	0.053	trace	0.010
2 weeks	C2 and C3	0.006	0.027	0.033	trace	0.007
2 months	C1 and C4	0.004	0.022	0.010	trace	0.002
Average		0.006	0.026	0.032	trace	0.006

* One cubic centimetre of Higgins *Waterproof* india ink per pound body-weight in a 1 to 4 dilution with physiological saline solution was injected into the femoral vein of the monkey.

† Each figure recorded is the mean of the analyses of two separate specimens of tissue.

does the spleen, this also being in accord with the deposition of tubercle bacilli.

The distribution of the bacilli alone cannot explain the monkey's organic susceptibility to tuberculosis, since the liver, in spite of the large amount of bacilli deposited in it, at times fails to develop any tuberculosis. In addition, the individual tubercles in the lung are the largest; those in the liver are the smallest of any in the five organs receiving appreciable amounts of bacilli; and the bone-marrow, which receives only slightly more bacilli than the lung, develops a disease far in excess of the amount which could be accounted for by the greater number of bacilli deposited in it.

SUMMARY

1. In summarizing the findings thus far presented, it appears that the importance of the deposition of the bacilli in the different organs of the four different species studied, as this deposition influences the tuberculous involvement of these organs, differs with the species. They may accordingly be divided into two groups.

2. In one group, the monkey and guinea pig, the quantitative distribution of living tubercle bacilli is of importance for the subsequent tuberculous involvement of the organs. These are the more susceptible animals. In them the amount of tuberculosis in the different organs is, in a general way, in accord with the amount of tubercle bacilli deposited in a given organ.

3. In the second group of more resistant animals, the rabbit and dog, individually differing quite markedly as to their characteristic organ involvement, the deposition of large amounts of bacilli in a given organ is not necessarily followed by a correspondingly large amount of tuberculosis. Thus, in the liver of the rabbit, in which there are deposited more bacilli than in the lung and much more than in the kidney, there develops less tuberculosis. Again, the spleen of the dog, in which there are deposited larger amounts of bacilli than in any other organ of the body, usually escapes macroscopic tuberculosis.

4. But even in the first group of susceptible animals, the monkey and guinea pig, the distribution of tubercle bacilli in the organs is alone insufficient to explain the organic tuberculosis in these animals. It cannot explain the preponderance of the disease in the guinea pig's lung over its hepatic involvement during the first 4 weeks after the intravenous inoculation of living tubercle bacilli, in spite of the fact that a far greater quantity of bacilli is deposited in the liver than in the lung. In the monkey it cannot explain the large size of the tubercles in the lung and the occasional absence of tuberculous involvement of the liver, in spite of the fact that the distribution of the bacilli to these two organs is the same as that in the guinea pig. Therefore, other additional factors must be sought for, in order to account for the susceptibility of the various organs to tuberculosis in the four species of animals under consideration.

Dr. Saul Mebel, Miss Rose Silver and Mr. Isadore Soifer kindly assisted in the technical work of this study.

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FIGURES

Description of Figures

FIG. 1. Photomicrograph of lung of rabbit three hours after intravenous injection of 1 cc. of india ink per pound body-weight. Note carbon in alveolar but not in bronchial walls.

FIG. 2. Photomicrograph of lung of rabbit 23 days after intravenous inoculation of 0.01 mgm. of virulent bovine tubercle bacilli and 1 cc. of india ink per pound body-weight. Note tubercle in lung, with epithelioid cells containing carbon.

FIG. 3. Photomicrograph of lung of rabbit 23 days after intravenous inoculation of 0.01 mgm. of virulent bovine tubercle bacilli and 1 cc. of india ink per pound body-weight. Note multiplication of subendothelial carbon-laden pericytes, gradually obliterating lumen of blood-vessel.

FIG. 4. Photomicrograph of lung of rabbit 23 days after intravenous inoculation of 0.01 mgm. of virulent bovine tubercle bacilli and 1 cc. of india ink per pound body-weight. Note perivascular origin of tubercle in lung, with obliterating endarteritis.

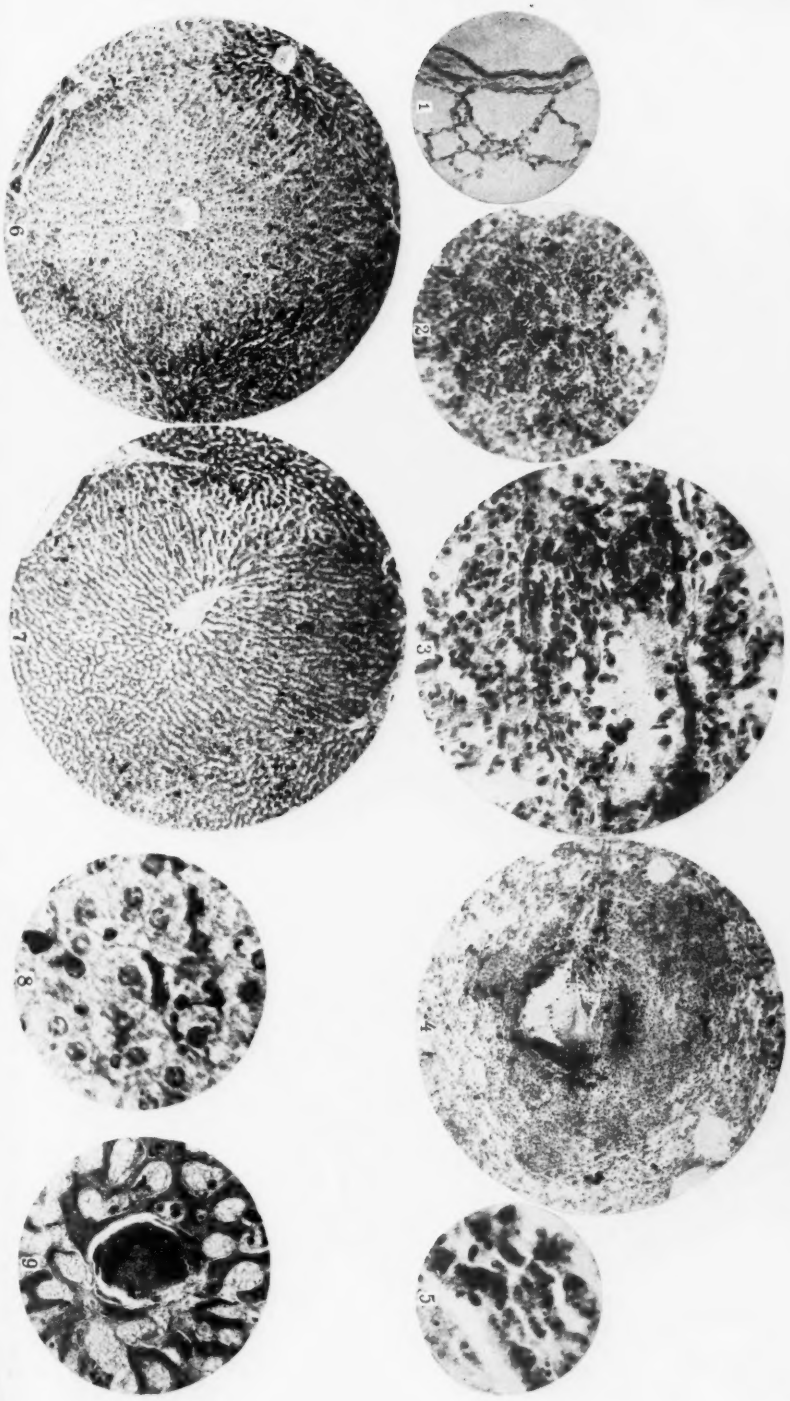
FIG. 5. Photomicrograph of lung of rabbit 24 days after intravenous inoculation of 0.001 mgm. of virulent bovine tubercle bacilli and 1 cc. of india ink per pound body-weight. Note tubercle bacilli and carbon particles in same cell.

FIG. 6. Photomicrograph of liver of rabbit immediately after intravenous injection of 1 cc. of india ink per pound body-weight. Note inflow of carbon at periphery of liver lobule.

FIG. 7. Photomicrograph of liver of rabbit 4 days after intravenous injection of 1 cc. of india ink per pound body-weight. Note distribution of carbon at periphery of liver lobule.

FIG. 8. Photomicrograph (high magnification) of liver of guinea pig 3 hours after intravenous injection of 1 cc. of india ink per pound body-weight. Note phagocytosis of carbon by Kupffer cells.

FIG. 9. Photomicrograph of liver of rabbit 50 days after intravenous inoculation of 0.000,01 mgm. of virulent bovine tubercle bacilli and 1 cc. of india ink per pound body-weight. Note tubercle in liver, consisting of single Langhans giant cell, with nuclei arranged in circle at periphery of cell and the carbon particles near the nuclei and surrounding a hollow sphere relatively free from carbon. This is a typical cell as described by Maximow.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Description of Figures

FIG. 10. Photomicrograph of spleen of rabbit 4 days after intravenous injection of 1 cc. of india ink per pound body-weight. Note carbon present predominantly in pulp of spleen.

FIG. 11. Photomicrograph (high power) of spleen of rabbit 73 days after intravenous inoculation of 0.000,01 mgm. of virulent bovine tubercle bacilli and 1 cc. of india ink per pound body-weight, showing Langhans giant cell containing carbon particles in ring formation. In such cells the tubercle bacilli are hidden by carbon particles.

FIG. 12. Photomicrograph of spleen of rabbit 50 days after intravenous inoculation of 0.000,01 mgm. of virulent bovine tubercle bacilli and 1 cc. of india ink per pound body-weight. Note tubercle in pulp of spleen, in which the centre contains relatively little carbon while the epithelioid cells are heavily laden with particles.

FIG. 13. Photomicrograph of kidney of rabbit one day after intravenous injection of 1 cc. of india ink per pound body-weight. Note deposition of carbon in glomerulus.

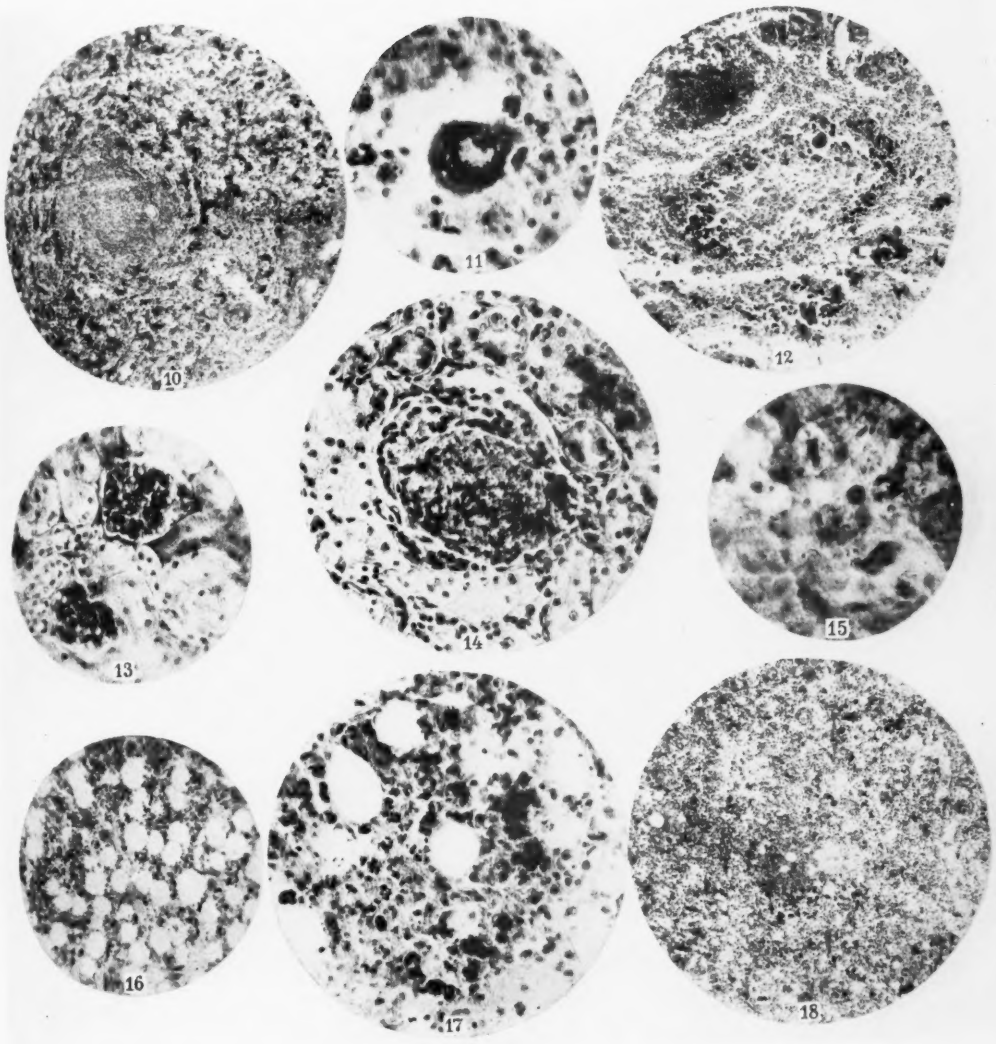
FIG. 14. Photomicrograph (high power) of kidney of rabbit 23 days after intravenous inoculation of 0.01 mgm. of virulent bovine tubercle bacilli and 1 cc. of india ink per pound body-weight. Note tubercle with necrotic centre originating in glomerulus.

FIG. 15. Photomicrograph of kidney of rabbit 24 days after intravenous injection of 0.001 mgm. of virulent bovine tubercle bacilli and 1 cc. of india ink per pound body-weight. Note tubercle bacilli and carbon in epithelioid cells.

FIG. 16. Photomicrograph of bone-marrow of rabbit one day after the intravenous injection of 1 cc. of india ink per pound body-weight. Note deposition of carbon in endothelial cells of sinuses.

FIG. 17. Photomicrograph (high power) of bone marrow of rabbit 13 days after intravenous inoculation of 0.1 mgm. of virulent bovine tubercle bacilli and 1 cc. of india ink per pound body-weight. Note tubercle with epithelioid cells of periphery more heavily laden with carbon than those in centre.

FIG. 18. Photomicrograph of bone-marrow of rabbit 25 days after intravenous inoculation of 0.01 mgm. of virulent bovine tubercle bacilli and 1 cc. of india ink per pound body-weight. Note absence of fat cells in parenchyma of bone-marrow and the enclosure of numbers of them within the tubercle. There is a breaking down of the walls of these fat cells as a result of necrosis, and a tendency for their fusion. The carbon is distributed around the periphery of the tubercle.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THE INHIBITIVE REACTION OF TUBERCULOSIS SERUM[1]

The Nature of the Inhibitive Substance

DAVID PERLA

In determining the antibody titre of the sera of horses, repeatedly inoculated with living tubercle bacilli grown on beef bile, Calmette and Massol (1) (2) (3) found that certain sera possessed the property of preventing the fixation of complement by antigen. These same sera were capable of exercising their inhibitive effect on other sera of known high antibody titre, preventing the complement-fixation reaction. Calmette and Massol were able to precipitate this substance with the euglobulin fraction by passing a current of carbon dioxide through the inactivated serum diluted with distilled water (3). Precipitins were brought down with the *inhibitrice* substance, while the agglutinins and complement-fixing antibodies remained in solution. The authors placed no practical value on the inhibitive reaction, however, since they were able only rarely to detect its presence in human sera (4).

Caulfeild (5) (6) (7) independently devised a method of determining the presence of this inhibitive substance in human serum. He found that the sera of certain tuberculous patients possess the property of inhibiting the fixation of complement by anticomplementary amounts of an alcoholic antigen derived from tubercle bacilli. After using this test with the tuberculo-complement fixation reaction for some years in the Toronto General Hospital, he feels that it is of some diagnostic and prognostic value in tuberculosis. My attention was directed to this reaction by the study of Caulfeild and his coworkers.

I undertook the study of the inhibitive reaction on human sera (1) to analyze the nature of the inhibitive phenomenon and (2) to estimate its value in clinical tuberculosis.

The Inhibitive Test

The method used was similar to that described by Caulfeild (5). Sera to be tested are inactivated, and used as in the tuberculo-complement-fixation reaction in the dilution of 0.1. The antigen is an alcoholic extract of tubercle bacilli. We prepared our antigen by

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia.

extracting during one week with absolute alcohol in a Soxhlet apparatus 2 gm. of human tubercle bacilli grown on glycerine-agar. The bacilli are dried in a desiccator for some days prior to extraction. The exact quantity of the bacillary bodies used in the extraction is of no importance as the titre of the antigen is carefully determined. The anticomplementary strength of the antigen is determined by preliminary tests against 2.5 units of complement in a total volume of 1 cc. of saline solution. The tubes are incubated during one hour at 37° before adding the hemolytic system. In the final inhibitive test four tubes are used for each serum. In the first tube is placed four times that amount of antigen which is just anticomplementary, in the second, twice that amount, in the third, exactly the amount of antigen that in itself fixes 2.5 units of complement, while the fourth tube is a serum control without antigen. The total volume in each tube is brought up to 1 cc. with physiological saline solution. The antigen is added to the serum before adding complement. The test is illustrated below (taken from Caulfeild (5)).

Example of the Inhibitive Test

Tubes for each serum	*1*	*2*	*3*	*4*
Serum	0.1	0.1	0.1	0.1
Antigen	0.1 (1/40)	0.1 (1/80)	0.1 (1/120)	0.0
Complement (2.5 units)	0.1	0.1	0.1	0.1

All tubes are brought up to a total volume of 1 cc. with physiological saline solution.

The tubes are incubated for one hour at 37°. The hemolytic system is then added, and the tubes are again placed in the water-bath at 37° for a half-hour. The hemolytic mixture is a 5 per cent suspension of packed, washed sheep-cells sensitized with antisheep-cell amboceptor. One-tenth of a cubic centimetre of the mixture contains 4 units of hemolysin. After the tubes are removed from the water-bath they are placed in the ice-chest, and the results are read and recorded the following morning.

The results are reported according to the scheme suggested by Caulfeild. Each of the four tubes is given a number from 0 to 4 depending on the degree of hemolysis, that is, inhibition of the antigen: 0 = complete hemolysis, 1 = almost complete hemolysis, 2 = partial hemolysis, 3 = slight hemolysis, and 4 = no hemolysis. The four numbers represent the results in the four tubes used in the test, reading from left to right, as follows:

4, 4, 4, 0	negative	negative results (normal)
4, 4, 2, 0, to 4, 3, 0, 0	third class	
4, 2, 0, 0	third class plus	
4, 1, 0, 0	second class minus	positive results
4, 0, 0, 0	second class	
3, 0, 0, 0	second class plus	
2, 0, 0, 0	first class minus	
C. H. to 1, 0, 0, 0	first class	

The complement-fixation reactions were carried out with Petroff's antigen in several dilutions of serum, or with an alcoholic and Petroff's antigens in one dilution of serum. In some of the tests two dilutions of Petroff's antigen were used, representing 40 and 10 minimal fixing units.

The inhibitive substance bears no relation to the antibody content of the serum. Calmette and Massol (2) found that the serum of goats,

repeatedly inoculated with bovine tubercle bacilli, which possessed a known high antibody titre, never gave this reaction. We were unable to demonstrate the inhibitive substance of sera of known high antibody titre obtained from goats and sheep that had received repeated injections of bovine tubercle bacilli. It was present in only small amounts in normal and tuberculous guinea pigs, and was occasionally present in tuberculous rabbits. Some degree of inhibition, comparable to what is found in normal human sera, is obtained with sera of normal rabbits.

It has been adequately demonstrated by Calmette (4) and by Hodge and MacLennan (8) that the euglobulin fraction of the serum contains the inhibitive substance. Hodge and MacLennan conclude that the inhibitive substance is a protein, which may be present in small amounts in normal serum but is increased in tuberculous serum.

SPECIFICITY

The specificity of the inhibitive reaction was tested by using, on the one hand, solutions of known protective colloids in place of serum, and, on the other, antigens other than an alcohol extract of tubercle bacilli.

Ten-per cent solutions of egg albumin, serum globulin, gum arabic, gelatine, and dextrin in physiological saline solution were prepared. Serum albumin dissolved with difficulty, and a saturated solution was less than 10 per cent. The anticomplementary titre was first determined, and the highest amount of the colloidal solutions used in each test was less than one-half the anticomplementary unit. It was found, as indicated in table 1, that gelatine in final dilutions as high as 0.001 gave a strong inhibitive reaction; gum arabic in dilutions from 0.01 to 0.001; egg albumin and serum albumin in dilution 0.001; serum-globulin solution in dilutions of 0.1 and 0.05. All these, when used in place of sera, inhibited the anticomplementary action of large amounts of an alcoholic extract of tubercle bacilli. It is significant that serum globulin gives the inhibitive reaction. A very slight degree of inhibition was obtained with diphtheria antitoxin, but not a positive reaction (see table 1).

In these experiments an attempt was made to use that amount of colloid that was approximately equal to the amount of serum globulins and albumins normally found in the blood serum. It is fully appreciated that the state of dispersion of the serum proteins is not entirely analo-

TABLE 1

The effect of protective colloidal solutions on anticomplementary doses of the alcoholic tuberculosis antigen (inhibitive test carried out with protective colloidal solutions in place of serum)

	INHIBITIVE REACTION	
Gelatin (saturated solution, less than 10 per cent)		
0.03 = 1/30	4, 1, 0, 0.	Positive
0.02 = 1/50	4, 0, 0, 0.	Positive
0.01 = 1/100	4, 0, 0, 0.	Positive
Gum arabic, 10 per cent solution		
0.1 = 1/10	3, 2, 0, 0.	Positive
0.05 = 1/20	4, 1, 0, 0.	Positive
0.01 = 1/100	4, 1, 0, 0.	Positive
Egg albumin, saturated solution		
0.05 = 1/20	4, 4, 4, 0.	Negative
0.01 = 1/100	4, 1, 0, 0.	Positive
Dextrin, 10 per cent		
0.2 = 1/5	4, 0, 0, 0.	Positive
0.1 = 1/10	4, 0, 0, 0.	Positive
Serum albumin (human), 10 per cent		
0.04 = 1/25	4, 4, 4, 0.	Negative
0.02 = 1/50	4, 4, 4, 0.	Negative
0.01 = 1/100	4, 0, 0, 0.	Positive
Beef serum albumin, 10 per cent		
0.1 = 1/10	4, 0, 0, 0.	Positive
0.05 = 1/20	4, 4, 4, 0.	Negative
0.01 = 1/100	4, 4, 4, 0.	Negative
Sheep serum globulin solution*		
0.1 = 1/10	4, 1, 0, 0.	Positive
0.05 = 1/20	4, 1, 0, 0.	Positive
0.02 = 1/50	4, 3, 1, 0.	Negative
0.01 = 1/100	4, 4, 4, 0.	Negative
Diphtheria antitoxin, diluted 1/10		
0.05 = 1/20	4, 4, 2, 0.	Negative
0.02 = 1/50	4, 4, 4, 0.	Negative
0.01 = 1/100	4, 4, 4, 0.	Negative

Note: The highest amount of colloidal solution used represents less than one-half the anticomplementary unit.

* The serum globulin was precipitated from sheep serum by adding an equal quantity of a saturated solution of ammonium sulphate. The solution was filtered, and the filtrate redissolved in distilled water, and the volume brought up to the original serum volume. The solution was dialyzed in a fish-skin bag against running tap-water until free from sulphate ions. It was then brought up to isotonicity.

gous to saline solutions of these colloids. From these experiments it may be concluded that the inhibitive phenomenon is due to the protective colloidal properties of the serum ingredients. Since it has been

adequately demonstrated by previous investigators that the inhibitive substance is bound up with the globulin content of the serum, it is probable that the serum proteins in certain concentrations act as protective colloids when added to the lipoidal colloidal solution used as antigen.

TABLE 2

The inhibitive test with other alcoholic antigens

SERUM	TUBERCULO-COMPLEMENT FIXATION	INHIBITIVE REACTION			
		Tuberculosis antigen	Lepra antigen	Kolmer's antigen	Petroff antigen
3	Negative	4, 1, 0, 0. Positive	4, 0, 0, 0. Positive	4, 1, 0, 0. Positive	4, 2, 0, 0. Negative
7	4+	4, 3, 0, 0. Negative	4, 4, 4, 0. Negative	4, 3, 0, 0. Negative	4, 4, 4, 0. Negative
9	3+	4, 0, 0, 0. Positive	4, 1, 0, 0. Positive	4, 0, 0, 0. Positive	4, 3, 0, 0. Negative
10	Negative	2, 0, 0, 0. Positive	1, 0, 0, 0. Positive	4, 0, 0, 0. Positive	3, 2, 0, 0. Positive

Note: The sera were all obtained from tuberculosis patients.

TABLE 3

Correlation between the tuberculosis and syphilitic antigens

SERUM	TUBERCULO-COMPLEMENT FIXATION	WASSERMANN	INHIBITIVE TEST	
			Tuberculosis alcoholic antigen	Kolmer's antigen
2 E. S.....	Negative	Negative	4, 4, 2, 0. Negative	4, 4, 3, 0. Negative
3 C. B.....	Negative	Negative	1, 0, 0, 0. Positive	3, 2, 0, 0. Positive
5 S. D.....	Negative	Negative	4, 4, 2, 0. Negative	4, 4, 2, 0. Negative
9 G. C.....	Negative	Negative	4, 1, 0, 0. Positive	4, 1, 0, 0. Positive
11 B. B.....	Negative	Negative	4, 4, 4, 0. Negative	4, 4, 3, 0. Negative
12 C. J.....	Negative	Negative	4, 4, 4, 0. Negative	4, 4, 3, 0. Negative
13 H. R.....	Negative	3+	4, 0, 0, 0. Positive	4, 4, 4, 0. Negative
14 E. O.....	Negative	Negative	3, 0, 0, 0. Positive	4, 0, 0, 0. Positive

These experiments led us to believe that if the reaction were due to a protective colloidal phenomenon of the serum constituents, this same inhibitive quality might be demonstrated on lipoidal colloidal sols other than one extracted from tubercle bacilli. We therefore used anticomplementary amounts of several alcoholic lipoidal solutions in exactly the manner of the inhibition test. Positive sera of tuberculosis patients were tested in this way with a nonspecific alcoholic tissue-extract (Kolmer's syphilitic antigen), an alcoholic extract of *Staphylococcus albus*,

an alcoholic antigen derived from *B. lepra* (Craig) and Petroff's water-glycerine extract of tubercle bacilli. The alcoholic tuberculosis antigen was used as a control (see tables 2, 3 and 4).

From the results indicated in tables 2, 3 and 4 it is evident that the inhibitive phenomenon is not a specific reaction. The results obtained with the leprosy antigen, Kolmer's antigen, and the alcoholic extract

TABLE 4

Correlation between the tuberculosis and Staphylococcus albus alcoholic antigens

SERUM	COMPLEMENT FIXATION			INHIBITIVE REACTION			
	Wassermann	Tuberculo-complement fixation	Staphylococcus complement fixation*	Tuberculosis antigen		Staphylococcus antigen	
116 J. F...	Negative	4+	Negative	4, 2, 0, 0.	Negative	4, 2, 0, 0.	Negative
117 V. B...	2+	2+	Negative	4, 3, 2, 0.	Negative	4, 4, 2, 0.	Negative
31 H.....	Negative	Negative	Negative	4, 1, 0, 0.	Positive	4, 0, 0, 0.	Positive
118 J. B...	Negative	Negative	Negative	4, 4, 2, 0.	Negative	4, 4, 0. 0.	Negative
105 M. K..	Negative	Negative	Negative	4, 2, 0, 0.	Negative	4, 2, 0, 0.	Negative
74 A. M..	Negative	Negative	Negative	4, 3, 1, 0.	Negative	4, 3, 0, 0.	Negative
28 A. T...	Negative	Negative	Negative	4, 3, 2, 0.	Negative	4, 4, 0, 0.	Negative
34 L. B...	Negative	Negative	Negative	4, 1, 0, 0.	Positive	4, 1, 0, 0.	Positive
62 R. R...	Negative	Negative	Negative	4, 2, 0, 0.	Negative	4, 0, 0, 0.	Positive
98 E. M..	Negative	3+	Negative	4, 3, 3, 0.	Negative	4, 2, 0, 0.	Negative
88 C. F...	4+	Negative	Negative	4, 2, 0, 0.	Positive	4, 3, 2, 0.	Negative
81 F.....	Negative	Negative	Negative	4, 1, 0, 0.	Positive	4, 1, 0, 0.	Positive
36 P.....	Negative	4+	3+	4, 4, 4, 0.	Negative	4, 4, 4, 0.	Negative
35 D.....	Negative	Negative	Negative	4, 4, 2, 0.	Negative	4, 4, 1, 0.	Negative
34 M.....	Negative	4+	Negative	4, 4, 2, 0.	Negative	4, 4, 0, 0.	Negative
33 D.....	Negative	4+	3+	4, 4, 4, 0.	Negative	4, 4, 3, 0.	Negative
32 W.....	Negative	4+	2+	4, 4, 4, 0.	Negative	4, 4, 2, 0.	Negative
31 H. A...	Negative	4+	Negative	4, 4, 4, 0.	Negative	4, 3, 0, 0.	Negative
28 E. R...	Negative	Negative	Negative	4, 1, 0, 0.	Positive	4, 0, 0, 0.	Positive

* Complement-fixation reactions were carried out with the alcoholic extract of the Staphylococcus albus simultaneously with the tuberculo-complement fixation tests.

of *Staphylococcus albus* correspond closely to those obtained with the tuberculosis alcoholic antigen. The water-glycerine extract of tubercle bacilli (Petroff's antigen) was inhibited only by very strongly inhibitive sera. From these results it may be concluded that a specific antigen is not essential in the demonstration of the inhibitive substance. These alcoholic extracts contain lipoidal substances in colloidal suspension, and it is to be expected that they will react in the same manner to solutions of protective colloids. The inhibitive reaction therefore cannot be considered to represent an antibody-antigen reaction.

RELATION OF THE INHIBITIVE PHENOMENON TO COMPLEMENT FIXATION

With tuberculous serum the complement-fixation reaction was usually negative or weak when the inhibitive test was positive. With the removal of the inhibitive substance Calmette (3) found that the tuberculo-complement-fixing antibody becomes demonstrable. I have found that if tuberculous serum, giving a positive inhibitive test and a negative tuberculo-complement fixation, is permitted to stand for a few days at ice-box temperature, the inhibitive quality of the serum diminishes or

TABLE 5

Relation of the inhibitive reaction to the tuberculo-complement fixation reaction

SERUM	TESTS ON FIRST DAY			TESTS ONE WEEK LATER		
	Complement fixation		Inhibition	Complement fixation		Inhibition
	Petroff antigen	Alcoholic antigen		Petroff antigen	Alcoholic antigen	
1. Tuberculosis 3B	2+	0	4, 0, 0, 0. Positive	4+	3+	4, 2, 1, 0. Positive
2. Tuberculosis 3A	0	0	3, 1, 0, 0. Positive	4+	2+	4, 2, 0, 0. Negative
3. Tuberculosis 3B	0	0	4, 1, 0, 0. Positive	0	0	4, 1, 0, 0. Positive
4. Tuberculosis 2A	0	0	4, 1, 0, 0. Positive	2+	1+	4, 2, 1, 0. Negative
5. Tuberculosis 3B	0	0	4, 0, 0, 0. Positive	4+	4+	4, 4, 3, 0. Negative
6. Tuberculosis 3A	0	0	3, 0, 0, 0. Positive	2+	3+	4, 4, 3, 0. Negative
7. Tuberculosis 3A	1+	0	4, 1, 0, 0. Positive	4+	4+	4, 4, 3, 0. Negative
8. Tuberculosis 3B	0	0	1, 0, 0, 0. Positive	2+	2+	3, 1, 0, 0. Negative
9. Tuberculosis 2A	4+	4+	4, 4, 4, 0. Negative	4+	4+	4, 4, 4, 0. Negative
10. Tuberculosis 2A	2+	0	3, 0, 0, 0. Positive	4+	4+	4, 3, 2, 0. Negative
Control negative	0	0	4, 4, 3, 0. Negative	0	0	4, 4, 3, 0. Negative

Note: Between 20 and 30 minimal fixing units of antigen were used in performing the tuberculo-complement fixation tests.

4+ = complete fixation; 0 = complete hemolysis.

disappears but the complement-fixing antibody generally appears (see table 5). From the results indicated in table 5, it would seem that the same substance that inhibits the anticomplentary amounts of an antigen may inhibit the smaller amounts of antigen used in complement fixation. This was particularly true when an alcoholic extract of tubercle bacilli was used in the complement-fixation reaction. Removal of the inhibitive substance permits the otherwise inhibited antigen to fix complement in the presence of the specific antibody, as Calmette has previously demonstrated. VonWedel first observed that it is possible to

increase the percentage of positive tuberculo-complement fixations by allowing the sera to stand several days in the ice-chest. Von Wedel (21), in describing this peculiar property of tuberculous serum, insists that no report should be made on the complement-fixation reaction until the serum has been tested after having been kept under sterile conditions in the ice-chest for from four to six days. By this method his

TABLE 6

Relation of the inhibitive reaction to the titre of the complement-fixing antibody

SERUM	WASSERMANN	TUBERCULO-COMPLEMENT FIXATION										INHIBITIVE REACTION	
		P. 0.1	A. 0.1	P. 0.05	A. 0.05	P. 0.02	A. 0.02	P. 0.01	A. 0.01	P. 0.005	A. 0.005		
L. C.	Negative	4	0	4	0	3	0	2	0	4	0	4, 1, 0, 0.	Positive
R. D.	4+	4	4	4	4	4	4	4	4	4	4	4, 4, 4, 0.	Negative
F. M.	Negative	0	0	0	0	0	0	1	0	2	1	4, 1, 0, 0.	Positive
A. E.	Negative	4	0	4	0	4	0	4	4	4	4	4, 4, 3, 0.	Negative
C. K.	Negative	0	0	4	0	4	3	—	—	—	—	4, 4, 0, 0.	Negative
R. G.	4+	0	0	0	0	0	0	0	0	0	0	4, 3, 1, 0.	Negative
T. W.	Negative	4	4	4	4	4	4	4	4	3	4	4, 4, 4, 0.	Negative
F. B.	Negative	0	0	±	0	±	1	3	4	3	4	4, 0, 0, 0.	Positive
A. C.	Negative	0	0	2	0	3	1	4	2	4	2	4, 0, 0, 0.	Positive
J. S.	Negative	3	0	4	0	4	0	4	1	4	3	4, 1, 0, 0.	Positive
C. B.	Negative	4	0	4	4	4	4	4	4	4	4	4, 4, 4, 0.	Negative
M. C.	Negative	0	0	1	0	3	0	—	—	—	—	4, 4, 1, 0.	Negative
M. H.	Negative	0	0	0	0	4	2	—	—	—	—	4, 4, 3, 0.	Negative
L. M.	4+	0	0	1	1	4	4	—	—	—	—	4, 4, 4, 0.	Negative
Positive control	Negative	4	4	4	4	4	4	4	4	4	4	4, 4, 4, 0.	Negative

Note:

P = Petroff antigen, 1/8 the anticomplementary dose, 40 minimal fixing units.

A = Alcohol antigen, 1/6 the anticomplementary dose, 30 minimal fixing units.

4 = Complete fixation in the tuberculo-complement-fixation tests.

percentage of positive complement-fixation reactions in active tuberculosis increased to almost 100. He offers no explanation for the phenomenon. During this time the positive inhibitive serum will generally become negative. It will be noted in the latter section of this study that a combined strong complement-fixation reaction together with a positive inhibitive test occurred in only one instance of 142 tuberculous sera tested, although weak complement fixations appeared in a little more than a third of all the positive inhibitive reactions. It is evident, therefore, that the percentage of positive complement fixations in tuberculosis increases from 90 to 95 if the inhibitive substance is re-

moved. It is very probable, however, that the percentage of positive tuberculo-complement fixations in clinically nontuberculous individuals would increase correspondingly.

The significance of the presence of the inhibitive substance became evident when a series of dilutions of serum was used in the complement-fixation tests. When the complement fixation was carried out in five or six dilutions, it was occasionally found that a serum, which gave a positive inhibitive test and a negative complement fixation in the dilution of 0.1, gave a positive complement fixation in 0.05 or even 0.01 dilution of the serum (see table 6). When the inhibitive reaction was very strongly positive, dilution of the serum did not bring out a positive complement fixation. But with moderately positive sera this interesting phenomenon occurred. Here, too, the masking of the complement-fixing antibody in the usual dilution of serum was more evident when the alcohol extract was used as antigen than when Petroff's antigen was used. The practical significance of this phenomenon is clear. Tuberculo-complement-fixation tests carried out on one dilution of serum are not entirely dependable. The explanation of the nature of the phenomenon is, however, not clear. It is possible that dilution of a serum causes a diminution in the inhibitive substance, or that in these cases there is an excess of antibody. We have repeatly observed in this connection that normal rabbit serum gives a negative complement fixation in 0.1 dilution, but a strongly positive one in dilutions of 0.05 and less for a considerable range.

DISCUSSION

There is no adequate explanation of the anticomplementary action of antigens. Tissue-extracts and blood-serum that are anticomplementary are believed to contain sessile receptors of a third order in the Ehrlich sense, according to Sachs (9). Roemer (10) has also attributed the anticomplementary action of extracts of crystalline lens, retina and pigmented epithelium to complementophile groups. Others attribute the antihemolytic effect of organ and tissue-extracts to their lipoid content (Bang and Forssman (11)), as Landsteiner and v. Eisler (12) had demonstrated that lipoidal substances possess anticomplementary action. Wassermann and Citron (13) demonstrated the anticomplementary action of neutral fats, and Frouin (14) of olive oil and triolein. However, Landsteiner and Stankovic (15) failed to obtain fixation of complement with cholesterin acetate or benzoate. We were unable to use in the

inhibitive phenomenon cholesterinized syphilitic antigen, since the range between the anticomplementary and hemolytic units was too small.

To understand the interaction of two substances, the nature of each must be known. According to Wells (16), complement is presumably a protein, for it has antigenic properties, so that immunization with sera containing either complement or complementoid causes anticomplementary activity in the blood of the immune animal, as was first demonstrated by Ehrlich and Morgenroth (17). Michaelis and Skwirsky (18) found that it is destroyed by trypsin free from lipase and, like other colloids, is readily adsorbed by surfaces. The colloidal nature of complement is further demonstrated by the observation of Schmidt (19) that it diminishes in amount when passed through Berkefeld filters.

According to Ehrlich's well-known theory, complement-like toxins and enzymes possess at least two groups: one, the haptophore, by which it unites with amboceptor; the other, the toxophore or zymophore, which unites with antigen. The fixation of complement by antigen is an irreversible reaction. It may be supposed that the antigenic molecules, in excess, attach themselves to the haptophore group of the complement, preventing its subsequent union with amboceptor. This is the hypothesis advanced by Ehrlich and Morgenroth (17) for the action of "anticomplement," produced by the injection of active horse-serum into goats. A more plausible explanation is offered by the observation of Michaelis and Skwirsky (18) that, in common with other colloids, complement is readily adsorbed by surfaces. The anticomplementary effect of large amounts of antigen is probably due to the adsorption of the complement by the surface of the complex antigen molecule.

Calmette (4) believes that the formation of the inhibitive substance in animals repeatedly injected with tubercle bacilli results from an over production of antibodies, and is associated with an increase in the globulin content of the blood. From the studies indicated in our paper, it would appear that the inhibitive phenomenon is dependent on the protective colloidal action of the constituents of serum, most probably the proteins.

Unable to obtain this reaction except in certain tuberculous sera in animals and in the presence of a specific antigen, Calmette and Massol (4) state, in reference to the *inhibitrice*, "It therefore seems evident that this property is specific." In an early study, Caulfeild (3) speaks of the "inhibitin" as a specific substance in tuberculous sera. Our

studies clearly indicate that this reaction is nonspecific, and is in no sense an immunological reaction. Since sera of known high antibody titre fail to give this reaction, it is obviously not a pre-zone phenomenon.

Observations on a substance in immune horse-serum which interferes with complement fixation have been made by Zinsser and Parker (20) with pneumococcus antigen. They have found that certain antipneumococcus horse-sera, although showing strong precipitation reactions with pneumococcus antigen, do not sensitize similar antigens to complement fixation. They found that such sera not only failed to fix complement in the presence of antigen but, in addition to this, prevented complement fixation when added in small amounts to tubes of sensitized pneumococcus antigen. This phenomenon is probably due to the inhibitive substance under discussion.

CONCLUSIONS

1. The inhibitive reaction of tuberculosis serum is not specific; it is dependent on an increase of the protective colloidal constituents in the serum.

2. Solutions of protective colloids used in place of serum inhibit anticomplementary amounts of an alcoholic antigen derived from tubercle bacilli.

3. The inhibitive substance in sera may be demonstrated by using nonspecific alcoholic lipoidal solutions as antigens in place of an alcoholic extract of tubercle bacilli.

4. The inhibitive substance in tuberculosis serum interferes with the fixation of complement in the tuberculo-complement-fixation reaction.

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THE INHIBITIVE REACTION OF CAULFEILD[1,2]

A Study of Its Clinical Value in Pulmonary Tuberculosis

DAVID PERLA

In an analysis of the nature of the inhibitive reaction of tuberculosis serum, reported in a preceding paper (1) it was found that the phenomenon is dependent upon an increase of the protective colloidal constituents in the serum, and is not specific. In estimating the value of the inhibitive reaction in pulmonary tuberculosis, the sera of tuberculous, of clinically nontuberculous and of clinically normal patients were tested.

With serial tests Caulfeild (2) was able to obtain a positive inhibitive test in 56.9 per cent of 265 clinically tuberculous patients. Positive or weak tuberculo-complement-fixation reactions were found in 76.9 per cent. From the results expressed in his tables, 76 per cent of the tuberculosis patients gave a negative inhibitive reaction to any one test, and positive reactions to any two tests were obtained in only 18 per cent of the series. Unfortunately, we were unable to make more than a single test in any one instance. Our results are therefore not quite comparable to those of Caulfeild's. We felt, however, that if we carried out the test in a large series of clinically nontuberculous patients suffering with other diseases, and in a large series of normal individuals, a conception of the relative value and frequency of the reaction might be obtained. Further, we tested the reaction in a series of clinically nontuberculous normal children, in whom tuberculin sensitiveness was determined. The results of these studies are presented in the tables.

CLINICALLY TUBERCULOUS INDIVIDUALS (147)

As table 1 indicates, a strongly positive or weakly positive tuberculo-complement-fixation reaction was obtained in 77 per cent of our patients. The inhibitive reaction was positive in only 25 per cent of the cases. It

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia.

[2] A description of this reaction is given in detail in the preceding paper, *American Review of Tuberculosis*, 1926, xiv, 706.

is significant, however, that the complement-fixation reaction was negative in two-thirds of the positive inhibitive instances. In only one instance were a strong complement-fixation reaction and a positive inhibitive reaction obtained in the same serum. In only 6 per cent of tuberculosis cases was neither a positive inhibitive nor a positive complement-fixation reaction present. From results with the complement-fixation reaction reported by numerous investigators there is a definite

TABLE 1

The inhibitive reaction

TOTAL	DEFINITELY POSITIVE CLINICAL TUBERCULOSIS (PULMONARY), 142 CASES	CLINICALLY NONTUBERCULOUS WITH OTHER DISEASES, 261 CASES	CLINICALLY NONTUBERCULOUS NORMALS, 119 CASES
	per cent	*per cent*	*per cent*
Inhibitive reaction			
1. Positive	25 (35)	18 (46)	16.8 (20)
2. Normal (negative)	75 (107)	82 (215)	83.2 (99)
Tuberculo-complement fixation			
1. Strongly positive[1]	54 (76)	13 (35)	21 (25)
2. Weak fixation[2]	23 (33)	29 (76)	22 (27)
3. Positive or weak	76.7 (109)	42 (111)	43 (52)
4. Negative	23.3 (33)	58 (150)	57 (67)
Combined reactions			
1. Positive inhibitive, strongly positive t. c. f.	0.7 (1)	0 (0)	1 (2)
2. Positive inhibitive, weak t. c. f.	9 (13)	4 (11)	4 (5)
3. Total combined reactions	10 (14)	4 (11)	5 (7)
Negative t. c. f. and positive inhibitive	15 (21)	14 (35)	10 (12)
Negative t. c. f. and negative inhibitive in the same test	6 (9)	44 (115)	44 (53)

[1] Complete fixation of 2.5 units of complement.

[2] Weak fixation is less than complete fixation.

group of tuberculosis patients whose sera give negative complement-fixation reactions. It is generally conceded that this group comprises 15 to 20 per cent of tuberculosis patients. The inhibitive phenomenon is responsible for a large proportion of the negative complement-fixation reactions in active tuberculosis. There did not seem to be any relation between extent of disease, activity, and the positive inhibitive test, although a somewhat larger number was found in the advanced cases of tuberculosis.

The earlier study has shown that aging of the sera in cases with a positive inhibitive test will increase the percentage of positive tuberculo-complement-fixation reactions to over 90.

It is apparent, therefore, that the inhibitive substance prevents the interaction of small amounts of antigen with antibody, as well as preventing the interaction of anticomplementary amounts of antigen and complement. If an alcoholic extract of tubercle bacilli is used as the antigen in the tuberculo-complement-fixation reaction, the correlation of a negative complement-fixation reaction and a positive inhibitive reaction becomes still more constant. Although of little diagnostic value in a single test, the inhibitive reaction is of considerable importance in explaining a hitherto baffling problem, and, together with the estimation of the complement-fixing antibody titre, gives a more comprehensive conception of the serological phenomena of tuberculous sera.

THE INHIBITIVE REACTION IN OTHER DISEASES

We have found that the inhibitive reaction appears positive in many conditions other than clinical tuberculosis. Of a series of 261 sera obtained through the courtesy of Dr. John Paul of the Pennsylvania Hospital from cases presenting no evidence of clinical tuberculosis but suffering from other diseases, positive inhibitive reactions were obtained in 18 per cent, that is, only slightly less than in clinical tuberculosis. A negative complement fixation and a negative inhibitive test were present in about 45 per cent of these patients in contrast to about 5 per cent in tuberculous individuals.

Pneumonia: Of 26 instances of bronchopneumonia or lobar pneumonia, a positive inhibitive phenomenon was present in 8, or 31 per cent. In lobar pneumonia there is apt to be an increase of serum proteins. There is often a relative increase in the serum globulin-albumin ratio. This perhaps accounts for the appearance of a protective colloidal phenomenon.

Fractures: It is interesting that, of 22 cases of fractures of the long bones in individuals otherwise in good health, 8, or 36 per cent, gave a positive reaction. These figures are somewhat higher than those found with single tests in tuberculosis.

Occasionally there were positive reactions in carcinoma, rheumatic fever and in gall-bladder disease. Several cases of appendicitis were positive. The remainder of the positive results were scattered among various acute and chronic diseases.

Syphilis: Because of the frequency with which tuberculo-complement-fixation reactions are positive in the presence of a positive Wassermann, it was thought advisable to test the inhibitive phenomenon in a series of syphilitic cases. In our studies of the nature of the reaction we had found that the inhibitive phenomenon could be demonstrated with a nonspecific syphilitic antigen, such as Kolmer's antigen, both in syphilitic and tuberculosis patients.

In a series of 54 patients with uncomplicated syphilis obtained from our syphilis clinic, in whom a positive diagnosis of syphilis had been made by symptoms and the Wassermann reaction, a positive inhibitive test, carried out with an antigen prepared from tubercle bacilli, was demonstrated in 15 per cent (table 2). This is about the percentage found in the series of normal individuals. However, a negative Wassermann reaction and a positive inhibitive test occurred in 4 instances. Repeated

TABLE 2

The inhibitive reaction in syphilis

TOTAL CASES	POSITIVE INHIBITIVE	POSITIVE WASSERMANN*	POSITIVE T.C.F.	WEAK T.C.F.	COMBINED POSITIVE I. AND POSITIVE WASSERMANN	NEGATIVE WASSERMANN AND POSITIVE INHIBITIVE	NEGATIVE WASSERMANN AND NEGATIVE INHIBITIVE
54	15% (8)	93% (50)	7% (4)	59% (32)	7% (4)	7% (4)	0% (0)

* Positive Wassermann at the time the inhibitive test was done.

Wassermanns had at other times and subsequently been positive. But in this series of syphilitic sera there was no instance in which both the inhibitive and the Wassermann reactions were negative. It is apparent that a certain percentage of known positive syphilitic patients may give negative Wassermann reactions due to the interfering action of nonspecific protective colloidal substances in the serum which constitute the inhibitive substance.

CLINICALLY NONTUBERCULOUS HEALTHY INDIVIDUALS

Twenty per cent of 124 clinically normal individuals gave a positive inhibitive reaction with a single test. Approximately 20 per cent in this same group gave a strong tuberculo-complement-fixation reaction, and a total of 48 per cent gave faint or positive reactions. Of 74 children under fifteen, about the same percentage of positive inhibitive reactions and positive complement-fixation reactions occurred as in the

adult group. Caulfeild obtained positive reactions in only 6 per cent of 77 normal students.

CORRELATION BETWEEN SENSITIVENESS TO TUBERCULIN AND THE CAULFEILD INHIBITIVE TEST IN A SERIES OF 50 CLINICALLY NORMAL CHILDREN

A study of a group of children was undertaken to determine the relation of the inhibitive reaction to latent tuberculosis. These children were taken from a series of contact and noncontact cases. Of these 44 children, 30 gave a positive tuberculin reaction. The tuberculin reaction was carried out in three dilutions. The first test was performed with 0.01 mgm., the second with 0.1 mgm., and the third with 1 mgm. of old tuberculin. Of the 44, 16 gave positive tuberculin reactions with

TABLE 3

The inhibitive reaction and tuberculin sensitiveness in children

TOTAL	POSITIVE INHIBITIVE	POSITIVE T.C.F.	WEAK T.C.F.	COMBINED POSITIVE T.C.F. AND POSITIVE INHIBITIVE	NEGATIVE T.C.F. POSITIVE INHIBITIVE	NEGATIVE T.C.F., AND NEGATIVE INHIBITIVE
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Negative tuberculin (15) ..	0 (0)	7 (1)	21 (4)	0 (0)	0 (0)	51 (8)
Positive tuberculin (30)	30 (9)	30 (9)	10 (3)	7 (3)	20 (6)	40 (12)
Total (45).....	20 (9)	22 (10)	16 (7)	6 (3)	13 (6)	43 (20)

the smallest quantity of tuberculin. Of these, 25 per cent gave a positive inhibitive reaction in a single test. A negative complement fixation and a negative inhibition occurred in two instances. The same percentage of positive inhibitive reactions, however, was found in the group that reacted only to the second or third dilution of tuberculin. We were unable to find any definite correlation between the complement-fixing antibody titre and the degree of tuberculin sensitiveness. This has been repeatedly observed by other investigators.

Only 15 of this series gave a negative tuberculin reaction with the strongest dilution of tuberculin. In no instance was the inhibitive reaction positive. Seven cases, however, gave a positive tuberculo-complement-fixation reaction (see table 3).

CONCLUSIONS

1. The inhibitive reaction occurs almost as frequently in clinically nontuberculous patients who are suffering with other diseases, and in normal individuals who are clinically nontuberculous, as in the tuberculous.

2. The inhibitive reaction may be obtained in about 25 per cent of tuberculosis patients. The presence of a positive inhibitive test is accompanied by a negative or weakly positive complement-fixation reaction. The inhibitive substance prevents the interaction of small amounts of antigen with antibody, as well as preventing the interaction of anticomplementary amounts of antigen and complement.

3. An inhibitive reaction may be obtained in about 15 per cent of syphilitic patients. In a certain number of syphilitic patients the Wassermann reaction becomes negative in the presence of the inhibitive reaction.

4. On the basis of these studies the inhibitive test of Caulfeild does not appear to be a specific reaction for clinical tuberculosis.

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THE KAHN TEST FOR SYPHILIS IN TUBERCULOSIS

GEORGE C. STUCKY[1] AND W. B. HUNTLEY[2]

There are general similarities between tuberculosis and syphilis. Both diseases are chronic in nature, both show a tendency toward involvement of the lymph nodes, and both frequently cause only malaise and other indefinite clinical symptoms. It is of the utmost importance, therefore, that a test used as an aid in the diagnosis of syphilis should not give false positive reactions in tuberculosis.

As is well-known, the Wassermann test infrequently gives false reactions in certain tuberculous but nonsyphilitic conditions. Such reactions are believed to be due to "cross-fixation" of complement between tuberculosis and syphilis, since in both of these diseases lipoid antigens are employed in the complement-fixation test.

Although the Kahn test (6) also employs a lipoid antigen, the test is based on the principle of precipitation, and is free from the use of complement and the other ingredients of the hemolytic system. Furthermore, it is gaining a strong hold as a method for the serum diagnosis of syphilis. It appears to combine technical simplicity, comparative freedom from sources of error, and dependability as a diagnostic agent. This method has supplanted the Wassermann test in many hospital laboratories, and in such institutions as the Medical Department of the U. S. Navy (1) and the Michigan State Department of Health (2). In the latter institution alone, about 80,000 Kahn tests (without Wassermanns) have already been reported to physicians with satisfactory results (3). It has therefore seemed of importance to collect as much data as possible on the behavior of the Kahn test in tuberculosis, particularly as to whether it would give false positive reactions in certain stages of this disease.

We were able to find but two reports in the literature on the Kahn test in tuberculosis. Kilduffe (4) tested the sera of 70 tuberculosis patients with the Kahn test before it was perfected to its present state. He did not give complete data, and reported finding four positive Kahn

[1] Ingham Sanatorium, Lansing, Michigan.
[2] Howell Sanatorium, Howell, Michigan.

reactions, in two of which syphilis was a complication, while in the remaining two no evidence of syphilis was established. Keim and Kahn (5) reported negative reactions with the Kahn test in 122 cases of various forms of tuberculosis from which syphilis was excluded. Among these cases, 19 were of the cutaneous type; 59 were pulmonary; 31, bone and joint; 8, genitourinary; and 5, tuberculous laryngitis.

In the present study, 385 patients were tested by the Kahn method. They were inmates at the Ingham and Howell sanatoria. A small

TABLE 1

Classification of 374 nonsyphilitic sanatorium cases giving negative Kahn reactions

CLINICAL DIAGNOSIS		NUMBER OF CASES
Tuberculosis	Far-advanced pulmonary	120
	Moderately advanced pulmonary	79
	Incipient pulmonary	34
	Hilum and tracheobronchial (children)	91
	Lymph node (adults)	5
	Bone and joint	8
	Genitourinary tract	2
	Skin	1
	Phylctenular conjunctivitis	1
Total		341
Nontuberculous	Pneumonokoniosis	1
	Bronchiectasis	2
	Carcinoma of lung	1
	Chronic nontuberculous lung infection	6
	No clinical evidence of tuberculosis	23
Total		33

number were in the out-patient departments of these institutions. The Kahn tests were performed in the Bureau of Laboratories of the Michigan Department of Health. As already indicated, this Department has officially adopted the Kahn test, replacing the Wassermann, as a routine procedure. An opportunity was thus offered to determine the nature of the results of the Kahn test in tuberculosis, not in comparison with the Wassermann but in correlation with clinical findings.

Table 1 presents an outline of 374 cases giving negative Kahn reactions. These include 120 far-advanced pulmonary tuberculosis, 79 moderately advanced, and 34 incipient; also 91 hilum and tracheo-

bronchial tuberculosis limited to children, and the remaining cases of a miscellaneous character. Among the cases enumerated, particularly among the far-advanced pulmonary tuberculosis cases, there are found the usual number of complications, such as tuberculous laryngitis and enteritis.

Eleven patients gave positive Kahn reactions. These are believed to be of sufficient interest to list separately.

Case 1: Miss N. S., Kahn ++++; aged 20; far-advanced pulmonary. Definite history of syphilitic infection of three years' standing. No history of antisyphilitic treatment.

Case 2: Mr. E. M., Kahn +; single; aged 43; far-advanced pulmonary. Chancre in 1912; two courses of treatment, 1921, 1922, and three courses, 1923–1924.

Case 3: Mr. G. M., Kahn ++; married, aged 59; far-advanced pulmonary. X-ray shows complete fibrotic consolidation of right lung with beginning calcification of this fibrosis in lower lobe. Definite tuberculosis history since 1905. Denies venereal disease. Patient left sanatorium (Howell) before syphilitic infection could be established.

Case 4: Mrs. L. W., Kahn ++++; aged 39; far-advanced pulmonary. Denies venereal infection. *Family history:* Of ten children, three still-births; one died of brain abscess; one of convulsions; and one by accident. Of four living children, two are submental; one is epileptic and one is normal. No history of treatment for syphilis.

Case 5: Mr. H. M., Kahn +++; divorced; aged 37, far-advanced pulmonary. Third time at sanatorium. Denies venereal infection. Considered a "rounder."

Case 6: Mr. A. S., Kahn ++++; married; aged 28; far-advanced pulmonary. Admits chancre in 1920. Received five courses of mercury injections.

Case 7: Mr. W. A., Kahn ++++; married; aged 49; pulmonary syphilis. Chancre, 1901; claims chancre again in 1909, which was "burned off." No history of further treatment. Patient shows beginning *tabes dorsalis*, irregular pupils, generalized adenitis, knee and ankle reflexes absent.

Case 8: Mrs. D. B., Kahn varied from ++ to +; aged 44; far-advanced pulmonary; diabetes mellitus. Diagnosed on different occasions as latent syphilis and central-nervous-system syphilis. Two preadmission Wassermann tests +++. Patient now shows some inequality of the pupils. Somewhat exaggerated patellar reflexes, and the achilles reflex is difficult to obtain.

Case 9: Mr. W. K., Kahn +++; single, aged 39, far-advanced pulmonary. Gonococcus infection, age 21. Admits having had antisyphilitic treatment two years previously.

Case 10: Mr. B. P., colored, Kahn ++; married, aged 39; no children; wife had 3 miscarriages and one still-birth, and gives ++++ Kahn; far-advanced-pulmonary and intestinal tuberculosis. Gonococcus infection, age 18. No history of specific therapy.

Case 11: Miss M. A., Kahn ++ followed by two negative reactions; aged 20, far-advanced pulmonary and intestinal tuberculosis. No history or clinical evidence of venereal disease. It is believed that the ++ finding was due to confusion of specimens.

It is evident that of the 11 patients giving positive Kahn reactions, 7 gave unquestionable evidence of syphilitic infection and two (cases 5 and 8) gave probable evidence of infection. Of the remaining 2 patients, one (case 3) gave a 2-plus reaction, the correctness of which could not be checked on account of the fact that the patient soon left the sana-

torium. The other (case 11) gave a 2-plus reaction followed by two negative reactions, suggesting the possibility that the blood specimen in the first examination may have been confused with other specimens.

It may be of interest to mention that the incidence of coexisting tuberculosis and syphilis is comparatively small in these two Michigan sanatoria. Thus, of 352 cases diagnosed as tuberculosis only 10 were infected with syphilis, a total of 2.8 per cent.

It is believed that the Kahn test, due to its comparative simplicity, lends itself for use in tuberculosis sanatoria, particularly in those lacking extensive laboratory facilities and animals required by the Wassermann test.

SUMMARY

An attempt was made to determine whether tuberculosis affects the specificity of the Kahn test for syphilis. Three hundred and eighty-five cases (352 tuberculous and 33 nontuberculous) were tested by the Kahn method. Of this number, 374 patients free from syphilis gave negative reactions. One patient, also believed to be free from syphilis, gave a weakly positive reaction (++) followed by two negatives. Another giving a weakly positive reaction could not be checked clinically due to his leaving the sanatorium. The remaining 9 patients gave positive reactions. Of this number 2 gave suggestive and 7 definite evidence of syphilitic infection.

It appears from these results that the specificity of the Kahn reaction for syphilis is not affected by the presence of coincident tuberculous infection.

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